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ALBRIGHT'S SYNDROME

(POLYOSTOTIC FIBROUS DYSPLASIA WITH CUTANEOUS PIGMENTATION IN BOTH SEXES AND GONADAL DYSFUNCTION IN FEMALES)

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The relationship of the parathyroid gland to calcium metabolism had been known for many years, but it was not realized until 1926 that widespread decalcification of the skeleton can be produced by a functioning parathyroid tumor. This discovery provided a wealth of new information relative to the abnormal metabolism of bone and also furnished the clue to successful treatment of hyperparathyroidism by surgical extirpation of the tumor. In certain cases, however, the clinical picture was not entirely typical of hyperparathyroidism.[1] The bony lesions developed in childhood and were spotty or disseminated rather than generalized[2] and sometimes were predominantly unilateral.[3] Extraskeletal abnormalities, such as large areas of cutaneous pigmentation, were noted, and in females precocious puberty was an outstanding feature.[4] Three seemingly dissociated manifestations, namely, disseminated fibrosis of bone, cutaneous pigmentation and precocious puberty among females, completed a syndrome which Albright and his co-workers[5] described in 1937 and which since that time generally has been known as Albright's syndrome.

In addition to furnishing clinical, roentgenologic and pathologic evidence which established this condition as a fairly definite entity, Albright stated it could be differentiated from hyperparathyroidism.[6] Thus surgical exploration of the neck could be avoided. His theory of the causation of this disease, namely, that the manifestations arose as a result of a congenital developmental defect involving many types of tissue, is perhaps hypothetic, but it has not yet been superseded by anything more specific or enlightening.

Albright's original communication stimulated intense interest in the syndrome which now bears his name, and other investigators presented isolated cases they had observed personally and cited from the literature earlier cases which had been hidden under a veil of obscure terminology. Prominent among these investigators were Lichtenstein and Jaffe.[7] Their attention was focused particularly on the associated lesions of bones, for which they coined the term polyostotic fibrous dysplasia. They attempted to show that in all cases studied the nucleus of the disorder seemed to center in the bony lesions, which when widespread were

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1. Meyerding, H. W.: Cystic and Fibrocystic Disease of the Long Bones, Am. J. Orthop. Surg. **16**:253-276 (Sept.); 367-382 (Oct.) 1918.

2. Freund, E., and Meffert, C. B.: On the Different Forms of Non-Generalized Fibrous Osteodystrophy: The Localized, the Diffuse Monostotic, the Unilateral and the Monomelic Form, Surg., Gynec. & Obst. **62**: 541-561 (March) 1936.

3. Moehlig, R. C., and Schreiber, F.: Polyostotic Fibrous Dysplasia: Report of a Case with Unilateral Involvement, Am. J. Roentgenol. **44**:17-23 (July) 1940.

4. Borak, J., and Doll, B.: Halbseitige Recklinghausensche Knochenkrankheit mit Pubertas praecox, Wien. klin. Wchnschr. **47**:540-541 (April) 1934.

5. Albright, F.; Butler, A. M.; Hampton, A. O., and Smith, P.: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females: Report of Five Cases, New England J. Med. **216**:727-746 (April 29) 1937.

6. Albright, F.; Scoville, B., and Sulkowitch, H. W.: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation, and a Gonadal Dysfunction: Further Observations Including the Report of Two More Cases, Endocrinology **22**:411-421 (April) 1938.

7. (*a*) Lichtenstein, L.: Polyostotic Fibrous Dysplasia, Arch. Surg. **36**:874-898 (May) 1938. (*b*) Lichtenstein, L., and Jaffe, H. L.: Fibrous Dysplasia of Bone: A Condition Affecting One, Several or Many Bones, the Graver Cases of Which May Present Abnormal Pigmentation of Skin, Premature Sexual Development, Hyperthyroidism or Still Other Extraskeletal Abnormalities, Arch. Path. **33**:777-816 (June) 1942.

associated sometimes with one or more of the other manifestations of Albright's syndrome. At the present time many of the older terms, such as osteitis fibrosa disseminata and focal osteitis fibrosa cystica, have been replaced to some extent by the term Albright's syndrome or polyostotic fibrous dysplasia, or by both.

No useful purpose would be served by a further discussion of the historical events that led up to the newer conception of this disease. This material has been presented in many excellent articles which have appeared with increasing frequency since 1937. Two of the more recent and complete reviews were made by Neller [8] in 1941 and by Gorham and co-workers [9] in 1942. The last-named investigators tabulated data gleaned from recorded cases of Albright's syndrome as it appears in both its complete and its incomplete form. Our purpose in this paper is to add to their table the case of Shallard [10] and 6 cases encountered at the Mayo Clinic (outlined in the table).

REPORT OF CASES

CASE 1.—A white woman 35 years of age came to the clinic on Jan. 12, 1943.[11] During March 1942, in the second trimester of her third pregnancy, she had sustained a pathologic fracture of the right femur. This apparently had healed under ordinary methods of treatment, but it was followed by a foot drop on the same side. This in addition to the gradual enlargement of a known pelvic tumor made the patient seek medical advice at the clinic.

The salient features in the patient's past history were as follows: At the time of birth she had weighed 4 pounds (1,815 Gm.) and her twin brother 8 pounds (3,629 Gm.). At birth she had large brown spots on the right cheek, neck and posterior cervicothoracic region, as well as on both buttocks and the left thigh. She stated that she had grown and matured rapidly, her height at 10 years of age exceeding that of her twin by an inch (2.5 cm.). By the age of 14 she had attained her maximal height of only 4 feet, 11 inches (150 cm.). Her twin had continued to grow steadily until the age of 17, at which time he was 6 feet (183 cm.) in height. At the age of 7 years menstruation had begun; concomitant early enlargement of the breasts occurred. She had married at the age of 24 and subsequently had gone through three pregnancies.

Physical examination at the clinic revealed a short woman who had a protuberance of the lower part of the abdomen, a foot drop on the right side and large, irregular, deeply pigmented areas of skin in the locations previously mentioned (fig. 1). The right leg, in comparison with the left leg, was somewhat atrophied and was 2 inches (5 cm.) shorter. The achilles reflex was absent on the right side, and the Babinski sign was positive bilaterally.

Roentgenograms of the skeleton revealed lesions that were interpreted as being typical of osteitis fibrosa. The locations of these lesions are shown in figure 2. The greatest involvement was in the right lower extremity. The right femur showed evidence of a healed pathologic fracture in its middle portion. The concentrations of serum calcium, phosphorus, phosphatase, cholesterol and so forth were well within the limits of normal, indicating that the bony lesions were probably quiescent. The concentration of estrogen in the urine was normal.

Fig. 1 (case 1).—Pigmented areas (*a*) on buttocks, left thigh and right cervicothoracic region and (*b*) on chin, right mandibular and anterior cervical regions. The abdominal distention is the result of the underlying pelvic tumor.

At operation on January 14 a lateral incision below the trochanter of the right femur disclosed normal periosteum and a thinned cortex investing a central portion which was mottled red and grayish white and of a soft, cheesy consistency. Some of this tissue and a small portion of pigmented skin of the right buttock were removed for biopsy (fig. 3), and the observations were similar to those described in the subsequent cases.

At operation on February 1, a large mucinous cystadenoma was removed from the left ovary. Biopsy of the right ovary was performed and showed normal ovarian cortex.

The patient made an uneventful convalescence from both operations and was dismissed after a regimen of

8. Neller, J. L.: Osteitis Fibrosa Cystica (Albright), Am. J. Dis. Child. **61**:590-605 (March) 1941.

9. Gorham, L. W.; Campbell, E. H.; Howard, W. P.; Donhauser, J. L., and Rust, N. H.: Albright's Syndrome: A Group of Cases Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and a Gonadal Dysfunction, Clinics **1**:358-385 (Aug.) 1942.

10. Shallard, B. T.: Osteitis Fibrosa Disseminata, M. J. Australia **1**:558-560 (April 20) 1940.

11. This is a summary of a case previously reported in detail (Dockerty, M. B.; Meyerding, H. W., and Wallace, G. T.: Albright's Syndrome [Fibrous Dysplasia of Bones with Cutaneous Pigmentation in Both Sexes and Gonadal Dysfunction in Females], Proc. Staff Meet., Mayo Clin. **19**:81-88 [Feb. 23] 1944).

*A Tabulated Record of Thirty-Nine Cases of Albright's Syndrome in Its Complete Form**

Case	Author	Date	Age, Years	Sex	Duration, Years	Precocious Puberty	Pigmented Cutaneous Spots	Number of Fractures	Roentgenologic Diagnosis, O. F. C.	Biopsy Diagnosis, O. F. C.	Serum Calcium	Serum Phosphorus	Serum Phosphatase	Exploration of Parathyroid Glands, No Tumor Found
1	Weil: Klin. Wchnschr. **1**: 2114-2115 (Oct. 14) 1922..	1922	9	F	7½	+1½ yr.	+	8	+	..	..	..	..	0
2	Hirsch [15]	1929	30	M	22	0	+	Numerous	+	+	N	..	..	++
3	Priesel, R., and Wagner, R.: Ztschr. f. Kinderh. **53**: 146-161 (April 11) 1932; their case 1	1932	13	M	2	0	+	0	+	..	N	..	..	+
4	Priesel, R., and Wagner, R.: Ztschr. f. Kinderh. **53**: 146-161 (April 11) 1932; their case 2	1932	6¾	M	3 weeks	0	+	0	+	..	>	>	..	0
5	Gaupp, V.: Monatschr. f. Kinderh. **53**: 312-322, 1932; her case 2	1932	9	F	7	+9 yr.	+	Several	+	+	N	N	..	+
6	Stalmann, A.: Virchows Arch. f. path. Anat. **289**: 96-126 (April) 1933; his case 3	1933	8	F	3	+9 mo.	+	Several	+	..	N	N	..	0
7	Snapper and Parisel [12]	1933	10	F	3	+7 yr.	+	6	+	? Xanthomatosis	..	..	..	++
8	Goldhamer, K.: Fortschr. a. d. Geb. d. Röntgenstrahlen **49**: 456-481 (May) 1934	1934	9	F	7	+2 yr.	+	1	+	+	N	N	..	0
9	Hummel, R.: Röntgenpraxis **6**: 513-519 (Aug.) 1934; his case 1	1934	11	M	5	0	+	Several	? + Juvenile Paget's	? + Juvenile Paget's	..	..	..	0
10	Hummel, R.: Röntgenpraxis **6**: 513-519 (Aug.) 1934; his case 2	1934	9½	M	2	0	+	0	? + Juvenile Paget's	? + Juvenile Paget's	..	..	..	0
11	McCune and Bruch [17b]	1937	9	F	7	+2 yr.	+	Numerous	+	+	N	N	>	+
12	Albright and others;[5] their case 1.....	1937	23	F	15	+7 yr.	+	8	+	+	N	N	>	0
13	Albright and others;[5] their case 2.....	1937	39	F	29	+1 yr.	+	1	+	+	<	N	>	0
14	Albright and others;[5] their case 3.....	1937	3½	F	3	+4½ mo.	+	0	+	+	N	N	>	0
15	Albright and others;[5] their case 4.....	1937	8	F	4½	+3½ yr.	+	0	+	+	N	N	>	0
16	Albright and others;[5] their case 5.....	1937	10	M	6	0	+	3	+	+	N	N	>	++
17	Pagniez, P.; Plichet, A., and Fauvet, J.: Bull. et mém. Soc. méd. d. hôp. de Paris **54**: 733-736 (May 9) 1938	1938	36	M	33	0	+	5	+	..	N	..	>	0
18	Albright, Scoville and Sulkowitch;[6] their case 1..	1938	21	M	16	0	+	6	+	..	> N	> N	>	+
19	Albright, Scoville and Sulkowitch;[6] their case 2..	1938	14	M	12	0	+	1	+	+	N	N	>	+
20	Musser, H. H., and Barnwell, R., in discussion on Albright, Scoville and Sulkowitch,[6] pp. 420-421	1938	11	M	4	0	+	2	+	..	> N	< N	..	0
21	Braid;[16] her case 1.....	1939	11	M	9	0	+	Numerous	+	..	N	N	>	0
22	Braid;[16] her case 2.....	1939	3	F	1½	+2½ yr.	+	4	+	..	N	N	>	0
23	Summerfeldt and Brown;[18] their case 1.....	1939	10	F	7	+3 yr.	+	3	+	+	..	..	>	+
24	Summerfeldt and Brown;[18] their case 2.....	1939	6	F	4	+2 yr.	+	0	+	+	..	..	>	0
25	Robson, K., and Todd, J. W.: Lancet **1**: 377-380 (Feb. 18) 1939	1939	33	F	27	+7 yr.	+	Several	+	..	N	N	>	+
26	Mondor, H., and others: J. de chir. **53**: 593-624 (May) 1939	1939	14	F	7	+7 yr.	+	Numerous	+	+	N	..	>	0
27	Diez, J.: Prensa méd. argent. **26**: 1870-1897 (Sept. 27) 1939	1939	18	F	7	+5 yr.	+	Numerous	+	+	N	N	>	+
28	Nichols [24]	1940	31	M	24	0	+	Numerous	+	..	N	N	>	++
29	Shallard [10]	1940	18	F	10	+4 yr.	+	2	+	..	N	..	>	+
30	Neller [8]	1941	7	M	1	0	+	3	+	+	N	N	>	0
31	Stauffer, H. M.; Arbuckle, R. K., and Aegerter, E. E.: J. Bone & Joint Surg. **23**: 323-334 (April) 1941	1941	19	M	16½	0	+	3	+	+	N	N	>	+
32	Thomas, H. W.; Meredith, T. N., and Wunderly, H. L.: J. Pediat. **18**: 638-642 (May) 1941	1941	13	M	10	0	+	3	+	+	N	N	..	0
33	Gorham and others [9]	1942	14	M	6	0	+	2	+	..	N	N	>	0
34	Case 1†	1944	35	F	28	+	+	1	+	+	N	< N	N	0
35	Case 2†	1944	6	F	4½	+	+	1	+	+	N	N	N	0
36	Case 3†	1944	14	F	8	+	+	1	+	+	N	N	N	0
37	Case 4†	1944	3	F	1	+	+	Multiple	+	+	N	> N	N	0
38	Case 5†	1944	28	M	9	0	+	Multiple	+	+	N	< N	N	0
39	Case 6†	1944	10	M	3	0	+	1	+	+	N	N	N	0

* Part of this tabulation was compiled by Gorham and others.

† Of this paper.

List of Abbreviations: O. F. C., osteitis fibrosa cystica; N, normal; >, greater than normal; <, less than normal; +, present or done; 0, absent or not done; .., not recorded; ?, doubt as to diagnosis.

aluminum acetate had been started according to the method advised by Helfet.[12]

Comment.—This case is extremely interesting in that the patient had reached middle age before the bony disease manifested itself by the occurrence of the pathologic fracture of the right femur. Yet clinical and chemical studies one year later revealed that the pathologic process in the bones already had become quiescent. The onset of menses at the age of 7 years indicated premature sexual development. The fact that the patient grew faster than her twin brother but stopped growing at the age of 14, while he continued to grow until the age of 17, suggested

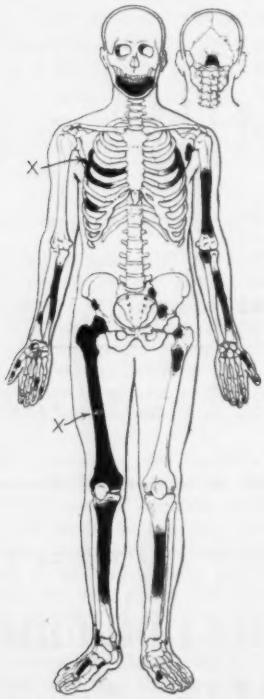

Fig. 2 (case 1).—Zones of fibrocystic involvement of bones (black areas). Sites of pathologic fractures are indicated by "X."

precocious somatic development followed by premature arrest of growth. The pigmented areas of the skin were large and well defined. The presence of a large mucinous cystadenoma of the left ovary, which was apparently coincidental, also adds to the interest of this case.

CASE 2.—A white girl 6 years of age was brought to the clinic on Aug. 7, 1942, because of a broken left leg. For three weeks she had been confined to her bed because the upper portion of the left leg had snapped under circumstances that suggested the presence of a pathologic process. Previous to this accident she had walked lamely on the left leg for two years.

The mother stated that the child had weighed 7 pounds (3,175 Gm.) at birth, that the neonatal period had passed without incident and that early growth and development had been normal. She had walked at the age of 1 year and talked at 18 months and had just completed her first year of school. She had suffered from scarlet fever, whooping cough, measles and mumps between the ages of 1 and 5 years, but none of these childhood diseases had been associated with complications.

The patient had had three episodes of vaginal bleeding, which had occurred at the ages of 1½ years, 2½ years and 3 years. When she was about 3 years of age, her mother had noted enlargement of both the child's breasts and the appearance of fine suprapubic hairs.

Physical examination revealed a thin girl who was irritable and definitely precocious. The breasts were developed to the extent expected in a girl of 16 years. There was a fine growth of axillary and pubic hair. The left leg, which was encased in a Thomas splint, was swollen and tender in its upper portion. Any movement of the leg produced severe pain. A large area of cutaneous pigmentation was present on the inner aspect of the left thigh. A napkin designed to protect the perineum against traumatic irritation by the splint was blood stained. The blood was found to be vaginal in origin.

The results of laboratory examinations were essentially negative. The concentrations of serum calcium and serum phosphorus were within normal limits, and the value for serum phosphatase was 3.9 Bodansky units. Roentgenograms revealed cystic disease of the entire left femur, with a pathologic fracture through a region of osteitis fibrosa located just below the greater trochanter. Some degree of periosteal reaction was evident. Similar zones of osseous rarefaction were noted in the region of the trochanter of the right femur, the right ilium, the left fibula and the left acetabulum (fig. 4). Roentgenograms of the skull, spinal column, left and right upper extremities and right lower extremity revealed no other abnormality except a bone age consonant with a chronologic age of 13 years.

Surgical exploration on August 13 revealed a pathologic fracture through a cystic cavity in the upper end of the left femur. The cavity, which was surrounded by a thin shell of cortical bone, was filled with blood clots and disorganized reddish gray tissue. Laboratory examination of some of this tissue ruled out the possibility of cancer. The existence of Albright's syndrome was suggested by the microscopic appearance of the fresh tissue, which was compatible with that of osteitis fibrosa. Accordingly the cavity was bridged by an autogenous bone graft removed from a healthy portion of the left tibia. The leg was immobilized by application of a cast.

Shortly after the operation the use of aluminum acetate was instituted, according to the method advised by Helfet, and this therapy was continued after the patient's dismissal. At the time of preparation of this report in August 1944, the parents had reported that the fracture had healed satisfactorily, but they had expressed concern over recurrence of the menstrual bleeding.

12. Helfet, A. J.: A New Conception of Parathyroid Function and Its Clinical Application: A Preliminary Report on the Results of Treatment of Generalized Fibrocystic and Allied Bone Diseases and of Rheumatoid Arthritis by Aluminum Acetate, Brit. J. Surg. **27**:651-677 (April) 1940.

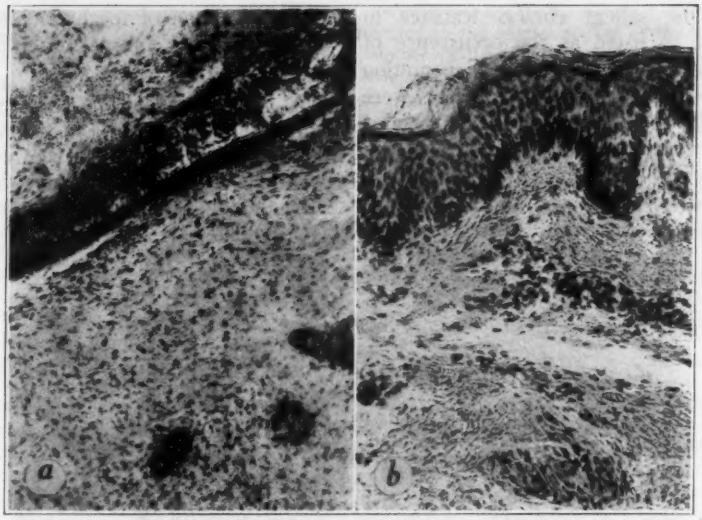

Fig 3 (case 1).—(*a*) Typical microscopic picture of bony lesions in Albright's syndrome showing extensive osteitis fibrosa with spicules of degenerating bone and no particular osteoclastic absorption (× 115); (*b*) lesion from the skin of the buttock showing pronounced hyperpigmentation of the basal layers of the epidermis and no suggestion of formation of nevus (× 165).

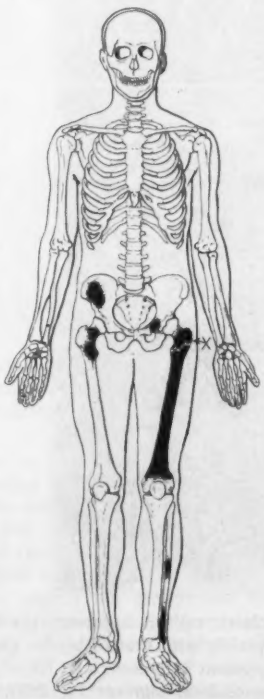

Fig. 4 (case 2).—Zones of fibrocystic involvement of bones (black areas). Site of pathologic fracture is indicated by "×."

The pathologic tissue was reddish gray, obviously infiltrated with blood, friable and gritty to palpation. Microscopically the basic element appeared to be spindle-shaped fibroblasts loosely or compactly arranged in a picture resembling osteitis fibrosa (fig. 5 *a*).

Three variations from this picture were noted: 1. In some areas giant cells were present in such abundance that a diagnosis of benign giant cell tumor appeared warranted from a study of isolated fields (fig. 5 *b*). Moreover, these giant cells contained as many as sixty to eighty nuclei and were indistinguishable from those encountered in typical giant cell tumor. This feature is in contrast to that generally reported in the literature: that is, that in polyostotic fibrous dysplasia giant cells are scanty or absent and when present demonstrate many atypical degenerated forms. 2. In other areas microscopic spicules of degenerating bone which did not appear to be surrounded by osteoclasts were present. Such an observation is in keeping with those of Jaffe. 3. Hemorrhage, old and recent, was everywhere in evidence, and where infiltration (fig. 5 *c*) of the tissues with hemosiderin was heaviest numerous foam cells appeared in small collections (fig. 5 *d*). In the past such a picture has been interpreted to mean that the entire process is on the basis of caseous xanthomatosis.[14] However, focal accumulations of foam cells occasionally may be found in any lesion in which hemorrhage leads to destruction of tissue. Their presence under these circumstances is on the basis of phagocytosis of lipoid material liberated after the disintegration of cells, and the postulation of a generalized condition of lipodystrophy becomes unnecessary.

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13. Snapper, I., and Parisel, C.: Xanthomatosis Generalisata Ossium, Quart. J. Med. **2**:407-417 (July) 1933.

14. Boenheim, C.: Frage der nervösen Komplicationen bei spezifischkindlichen Infektionskrankheiten und Vaccination, Klin. Wchnschr. **6**:1552-1555 (Aug. 13) 1927. Ford, F. R., and Guild, H:. Precocious Puberty Following Measles Encephalomyelitis and Epidemic Encephalitis, with Discussion of Relation of Intracranial Tumors and Inflammatory Processes to Syndrome of Macrogenitosomia Praecox, Bull. Johns Hopkins Hosp. **60**:192-203 (March) 1937.

Comment.—The salient clinical features in this case might be listed as the occurrence of precocious puberty and cutaneous pigmentation in association with osseous lesions which were not widespread. The impression one obtains from the literature is that the extraskeletal changes accompany only the most florid examples of polyostotic fibrous dysplasia. In this case almost the reverse was true. The unilateral character of the osseous lesions was in keeping with previously observed tendencies in Albright's syndrome. The presence on pathologic examination of typical giant cells of the osteoclastic type and of focal accumulations of foam cells constituted unusual observations.

CASE 3.—A white girl 14 years of age was brought to the clinic on Aug. 3, 1911, complaining of a tumor of the right forearm that had been present for one year. One month previously a specimen of the growth had been removed for biopsy and had been thought to reveal giant cell sarcoma. Amputation had been advised, but permission was refused by the parents. Eight years prior to admission the patient had sustained a pathologic fracture of the right humerus. Resection of the upper 3 inches (7.6 cm.) of the right radius was performed at the clinic on August 5 for a giant cell tumor. Convalescence was uneventful.

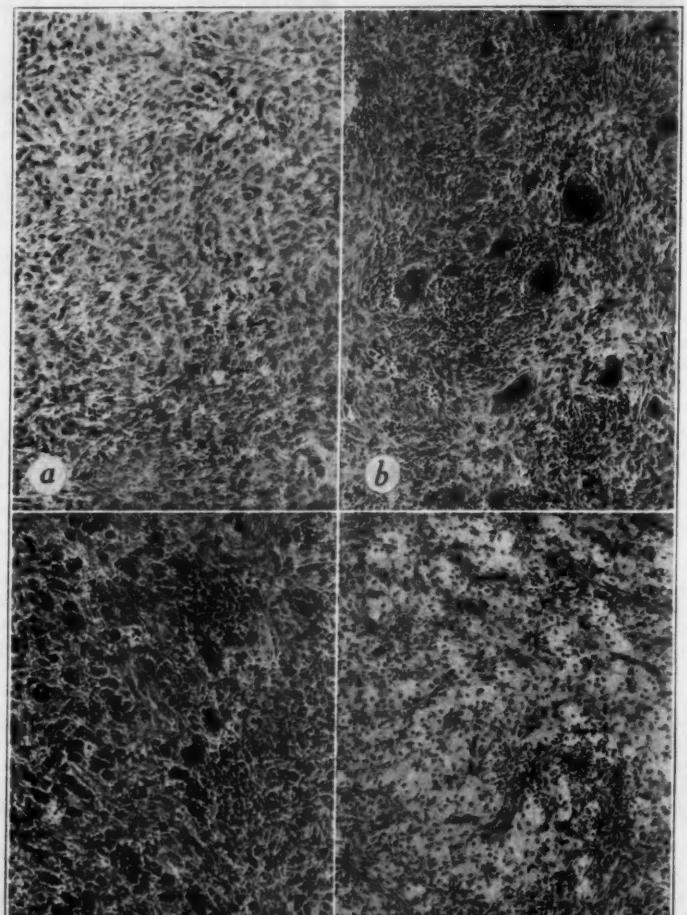

Fig. 5 (case 2).—(*a*) Widespread replacement of bone with fibroblastic cells is apparent; the tissue is relatively avascular (× 180). (*b*) Isolated zone presents a picture compatible with that of benign giant cell tumor of bone; the giant cells possess large numbers of nuclei; some blood pigment is present (× 110). (*c*) Degenerating spicules of bone appear in a fibrous matrix impregnated with hemosiderin pigment (× 200). (*d*) Isolated focus contains large numbers of foam cells; presence of these cells does not nullify a diagnosis of Albright's disease as was formerly thought (× 110).

The patient returned in 1918, complaining of a tumor of the forehead and of another in the region of the right ankle. Both tumors had been painless and had grown slowly. The clinical record includes brief descriptions of semisolid osseous tumors in the locations mentioned and of a thoracic scoliosis. Roentgenograms of the two bony lesions were interpreted as revealing osteitis cystica of rather pronounced degree. At operation on February 14, the cystic degeneration was found to involve apparently the entire diaphysis of the right tibia. The cortex was thin and trabeculated. Contents consisted of fibrous degenerating material and some bone. It varied in density from soft cartilage to osseous material. In some regions it could be removed by curettage, and in others it was necessary to use the chisel. On examination the tissue removed presented the picture of osteitis fibrosa.

The third admission of this patient to the clinic occurred in 1928. She complained of swelling of the upper portion of the right arm of fifteen months' duration.

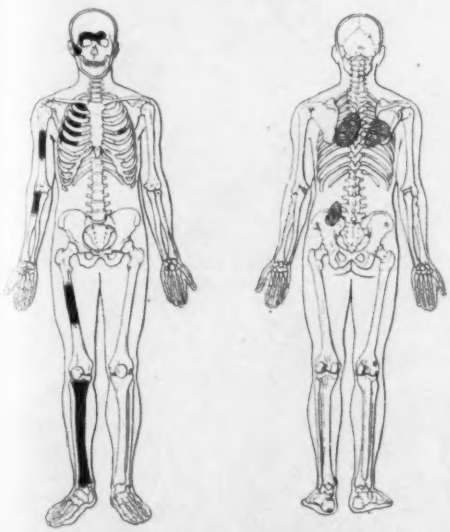

Fig. 6 (case 3).—Zones of fibrocystic involvement of bones (black areas). Shaded areas show distribution of pigmentation.

The condition had come on rather suddenly and had been accompanied in the early stages by local pain and disability. The patient's history was reviewed carefully at this time and the following information was added to the clinical record: Menstruation, which had begun when the patient was 11 years of age, had been normal for about six months but always had been irregular thereafter. No pertinent data were noted regarding other evidences of precocious puberty. However, the patient's height of only 4 feet, 9 inches (144.7 cm.) possibly represented precocious arrest of somatic development. In similar cases reported in the literature a short stature had been interpreted as being the end result of precocious changes in the bones. Four areas of cutaneous pigmentation were found on the patient's back. The largest of these, 3.2 inches (8 cm.) in diameter, was located over the lower angle of the left scapula. The other three areas were located on the left buttock, over the middle portion of the right scapula and on the back of the left thigh. A moderate degree of thoracic scoliosis was apparent. A tumor of osseous origin was located in the frontal region of the right humerus and another in the middle portion. There was no measurable shortening of any one of the four extremities, and the only limitation of motion observed was in the region of the operative scar around the right elbow joint.

Determinations of serum calcium revealed normal values. Roentgenographic studies of the bones of the extremities revealed lesions of the right humerus, right radius, right tibia and right femur which were interpreted as osteitis fibrosa. The lesion in the right humerus also showed evidence of an old incomplete fracture with some regional thickening of the bone in the area of clinical tumefaction. The right frontal region of the skull on roentgenographic study demonstrated changes similar to those present in the extremities.

Inasmuch as the bony lesions were causing no particular disability, operation was not urged, and the patient was sent home with instructions regarding a diet rich in minerals. She was advised to return if there was any adverse change in her condition.

The patient was last admitted to the clinic on Feb. 14, 1940. She sought advice concerning a tumor in the breast, which proved at operation to be benign.

Clinically the orthopedic condition appeared to be quiescent. The values for serum calcium and serum phosphorus were within normal limits, but that for serum phosphatase was slightly increased (6.8 Bodansky units). Roentgenographic studies of the bones previously examined revealed little change from earlier observations; however, a thorough roentgenologic review revealed lesions in the right ilium and first, second, third, fourth and fifth ribs on the right (fig. 6). A cystic area in the right zygomatic bone and increased density in the region of the frontal sinuses were noted. The only osseous lesion on the left side of the body was a small zone of rarefaction in the fourth rib. The patient was discharged without any special orthopedic treatment.

The pathologic material available for study consisted of the upper segment of the right radius and a few scrapings from the right tibia, both of which had been fixed for years in formaldehyde solution (10 per cent of the U. S. P. concentration). On gross examination of the radial lesion, the cortex was found to be of eggshell thinness and was expanded in the form of a thin capsule over a brownish gray mass of tissue which replaced both marrow and substantia spongiosa in the upper third of the bone. This mass measured 9 by 7 by 6 cm. and was of rubbery consistency but contained identifiable spicules of bone. It was solid throughout except for a small central zone of liquefactive softening. The lesion impinged on, but apparently did not invade, the epiphysial end of the radius, which, with the capitulum, was intact and firmly fused with the diaphysis proximal to the previously mentioned region of softening (fig. 7 *a*). Microscopic sections made from the various parts of the lesion and stained routinely with hematoxylin and eosin revealed pictures comparable in many respects to those described in case 2. In many areas the picture was typical of benign giant cell tumor. In others the appearance recalled that of osteitis fibrosa cystica with a paucity of osteoclasts. Spicules of degenerating bone were observed lying in zones which demonstrated little by way of reactive absorption. In addition, many areas of young osteoid tissue were surrounded by a ring of osteoblasts (fig. 7 *b*). Several small islands of young cartilage were encountered (fig. 7 *c*), but only an occasional foam cell was found. Blood vessels were in general few, but evidence of previous hemorrhage in the form of scattered de-

posits of hemosiderin was everywhere apparent. Sections similarly prepared from the tibial lesion duplicated for the most part the microscopic patterns of sections prepared from the radial lesion (fig. 7 *d*). No cartilaginous elements were observed in any of the sections.

The salient clinical features in this case were the long evolution of the disease with periods of exacerbation and of remission covering a period of thirty years and the recent clinical quiescence of the lesions in spite of chemical activity as evidenced by the high level of serum phosphatase. Whether the onset of menses at the age of 11 years represented actual sexual precocity and whether an ultimate height of 4 feet, 9 inches (144.7 cm.) actually indicated premature arrest of growth are questions that are perhaps somewhat equivocal.

CASE 4.—A white girl 3 years of age was brought to the clinic on July 30, 1928, because of a lump on the right leg and difficulty in walking for one year. The family history was noncontributory. The patient was the younger of two children; her sister always had been perfectly well. The patient's birth and early development had been normal, but when she was about 12 months of age the parents had noted that the right leg was shorter than the left. At the age of 18 months, when the patient had begun to walk, a limp of the right leg was evident. Shortly thereafter the parents had noted a small lump in the middle portion of the right thigh. Since birth there had been an area of discoloration on the back of the head, and this area had always been devoid of hair. The child always had been bright mentally.

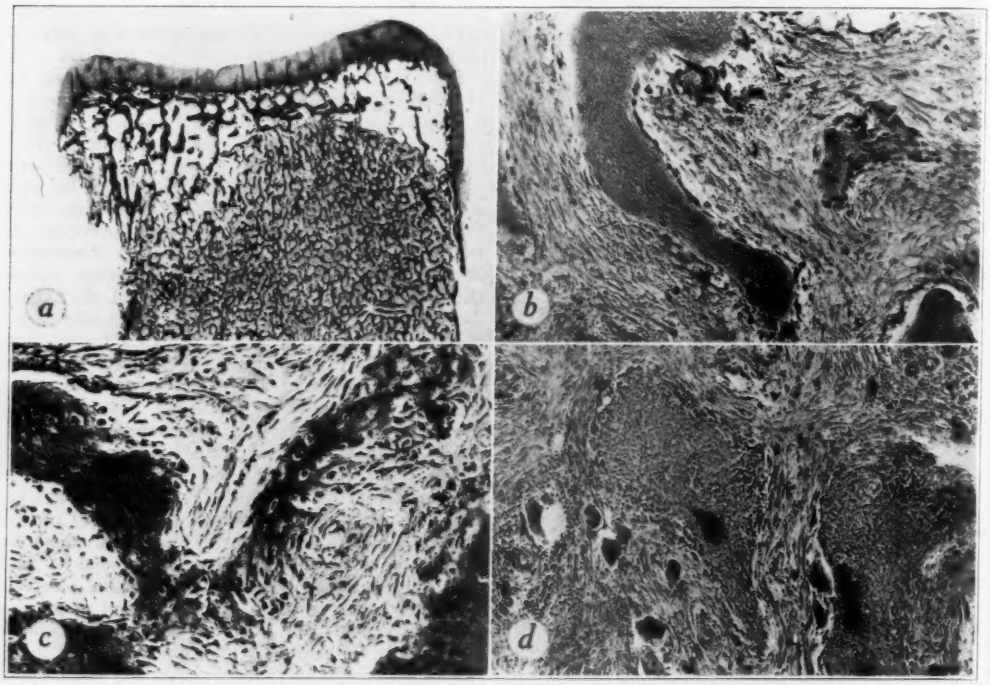

Fig. 7 (case 3).—(*a*) Upper end of the resected radius proximal to the "brown tumor" (note the intact appearance of the radial epiphysis) (× 4); (*b*) islands of osteoid tissue apparently surrounded by rings of dark-staining osteoclasts; some spicules of degenerating bone also present; osteoclastic activity minimal (× 100); (*c*) an island of cartilage in a zone of osteitis fibrosa cystica (× 180); (*d*) osteitis fibrosa of tibia with a fair number of giant cells (×100).

The osseous changes observed roentgenologically were almost exclusively on the right side, but the pigmented spots were located chiefly on the opposite side. This observation is recorded as being unusual, according to the literature on this bizarre disease.

Comment.—This case is unusual from the pathologic standpoint in that a local so-called brown tumor of bone was diagnosed and treated in a fairly radical manner as a giant cell tumor. These tumors are of rare occurrence in the cases of Albright's syndrome recorded in the literature.[7b]

Physical examination at the clinic revealed a well developed, well nourished child whose height was 3 feet, 2 inches (96.5 cm.) and whose weight was 33 pounds (15 Kg.). She walked with a limp that apparently resulted from the fact that the right leg was 1.6 inches (4 cm.) shorter than the left. Some atrophy of the right leg was also present, and mild genu valgum was apparent. A moderate degree of left thoracolumbar scoliosis was interpreted as being compensatory in nature. Motions of the afflicted limb apparently were not limited, and no pain was elicited on pressure. A large area of alopecia was present on the occipital region of the scalp, and the skin overlying this area was pigmented. There was no evidence of

facial asymmetry, but asymmetry was noted in the region of the vulva, with apparent hypertrophy of the right labial folds. Examination of the thorax gave a negative result, except that a loud systolic murmur was heard over the entire precordial region. This murmur was transmitted to the left axilla and back and was not accompanied by a thrill, and it was thought to be attributable to a congenital cardiac defect that was not of a serious nature.

Results of laboratory examinations were essentially negative. Roentgenograms of the right lower and right upper extremities were interpreted as giving evidence of osteitis fibrosa, with the suggestion of a pathologic fracture involving the upper end of the right tibia. No osseous change in the ribs was noted in roentgenograms of the thorax.

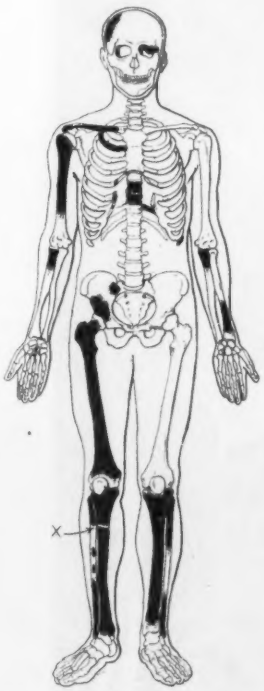

Fig. 8 (case 4).—Zones of fibrocystic involvement of bones (black areas). Site of pathologic fracture is indicated by "X."

The consensus was that the patient was suffering from multiple congenital developmental defects. Since no specific treatment was known at that time, the parents were advised to bring her back periodically for reconsideration and for such symptomatic treatment as might be indicated by complications resulting from a possible progression of the osseous lesions.

From 1928 to 1932, the patient made yearly visits to the clinic. Roentgenologically the osseous lesions appeared progressive in extent and severity, although there was little clinical disability. Complete absence of typical symptoms seemed to rule out a diagnosis of parathyroid tumor. The possibility of xanthomatosis was considered, but a biopsy in 1932 of the osseous lesion of the right tibia demonstrated the picture of osteitis fibrosa without the presence of foam cells.

In 1934, a pathologic fracture was sustained through cystic lesions involving the lower ends of the right tibia and fibula. Fixation was accomplished by means of homogenous grafts. Roentgenograms made at the clinic were interpreted as revealing pronounced fibrocystic disease involving the femur, ilium, tibia and fibula on the right, both arms, right clavicle and acromion of the right scapula, ninth and tenth thoracic vertebrae, pelvis, right sacroiliac and acetabular regions, second right rib and eleventh left rib (figs. 8 and 9). A considerable increase was noted in the extent of similar lesions of the skull in comparison with the degree of previous involvement (fig. 9 *b*). Some asymmetry was noted, the right parietal bone being thicker than the left. The value for serum calcium was 9.7 mg., for serum phosphorus 6.0 mg. and for serum phosphatase 6.2 Bodansky units, per hundred cubic centimeters.

The patient returned to the clinic in 1941. She had sustained a pathologic fracture of the right femur in 1937. Several attempts to secure proper fixation by the method of open reduction had been unsuccessful. An attempt to add information to the clinical record also revealed that she began menstruating shortly after her twelfth birthday.

Small fragments of tissue preserved in formaldehyde solution (10 per cent of U. S. P. concentration), which represented material removed from the tibia in 1932 and during the procedure of bone grafting in 1934, were available for study. Microscopic sections of both specimens stained with hematoxylin and eosin demonstrated the presence of osteitis fibrosa with a variable number of giant cells (fig. 10 *a*) and complete absence of foam cells. Some cartilage was present (fig. 10 *b*). In both specimens fragments of degenerating bone were present, as well as islands of osteoid tissue surrounded by zones of reactive osteoblasts. Considerable evidence of recent hemorrhage was evident in the tissue removed in 1934 from the site of the fracture but was absent in the specimen obtained for biopsy in 1932.

Comment.—In this case the history is of "bone trouble" that was slow in evolution, beginning in childhood and continuing through adolescence with exacerbations and remissions. It was accompanied by the occurrence of a peculiar area of pigmentation of the scalp associated with localized alopecia. The fact that the patient's height measured 3 feet, 2 inches (97 cm.) at the age of 3 years, 4 feet (122 cm.) at the age of 6 and only 4 feet, 5 inches (135 cm.) at the age of 15 might well indicate that an early acceleration of growth perhaps had been arrested prematurely. This observation is in accord with the observed phenomena of Albright's syndrome. Precocity completed the bizarre clinical picture, but this precocity, except for the labial hypertrophy, was characterized by early somatic rather than early sexual development. The observed value for serum phosphatase was probably lower than that expected, considering the extent and activity of the osseous lesions. The delayed union in the healing of the femoral fracture was perhaps unusual. Roentgenographic highlights consisted of the development of new lesions with a predilection for bones on

the right side, an increase in severity and extent of older lesions with maximal changes in the lower extremities, thickening of bones of the cranial vault and sparing of bony epiphyses.

CASE 5.—A white man 28 years of age was admitted to the clinic on July 6, 1937, complaining of a porous condition of his bones. The family history was not significant. Childhood diseases included measles, mumps, whooping cough and chickenpox, none of which was described as being particularly severe. He had had influenza in 1928 and gonorrhea in 1930. In 1929 the patient sustained a fracture of the left humerus when he attempted to lift a roll of rubber down from a shelf. Roentgenograms at that time revealed a cystic condition involving several bones. The fracture apparently healed. One year later the patient slipped and fell, again fracturing the left humerus. A third fracture of the same bone occurred in 1935 under circumstances which indicated the presence of a pathologic process. A cast was applied, and union was secured after a period of two months. The patient stated that he had cracked his ribs on many occasions, the first of these incidents occurring when he was 14 years of age. No positive information was elicited concerning the date of the onset of puberty.

Physical examination revealed a deformed, short man whose height was slightly more than 5 feet (152 cm.) and whose weight was 126 pounds (57 Kg.). Considerable outward bowing of the upper portion of the left arm was apparent. The left arm was 2.4 inches (6 cm.) shorter than the right. There were also well defined thoracic kyphosis and lumbar scoliosis. The patient had a barrel chest, and even when he assumed the standing position the lower ribs almost overrode the crests of the ilium. Two large areas of cutaneous pigmentation were noted over the region of the sacrum, one on each side. In addition, numerous freckles were scattered over the body. The external genitalia were normal except for the presence of varicocele on the left side. An enlarged thyroid gland constituted the only other important observation on clinical examination, which included a neurologic investigation.

Fig. 9 (case 4).—Lesions of disseminated osteitis fibrosa involving (*a*) right femur and right ilium, (*b*) right parietal and left temporal regions of skull, (*c*) and (*d*) right tibia and right fibula with two pathologic fractures of tibia, (*e*) right upper extremity and (*f*) left radius and ulna. Lesions are characteristically spotty in distribution and predominantly unilateral and demonstrate a notable sparing of epiphyses. For complete picture of skeletal lesions see figure 8.

Erythrocytes numbered 5,160,000 and leukocytes 7,400 for each cubic millimeter of blood. The value for hemoglobin was 15.3 Gm. per hundred cubic centimeters of blood. Urinalysis and the flocculation test revealed nothing abnormal. The value for serum calcium was 9.6 mg. per hundred cubic centimeters and for serum phosphorus 3.4 mg. per hundred cubic centimeters, and the activity of serum phosphatase was equivalent to 10.4 Bodansky units.

Roentgenograms, interpreted as showing the picture of osteitis fibrosa, showed lesions in the following locations: sternum, left scapula, third, fourth, fifth, sixth and seventh ribs on the left and seventh rib on the right (fig. 11); first metacarpus and entire radius on the left (fig. 12*a*); left humerus (fig. 12*b*), and eighth

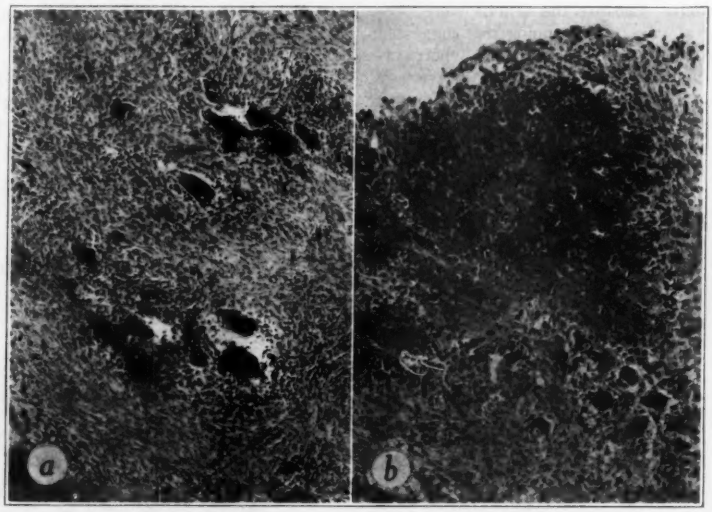

Fig. 10 (case 4).—(*a*) Osteitis fibrosa of tibia with a sufficient number of giant cells in certain areas to warrant a diagnosis of giant cell tumor (× 80); (*b*) islands of cartilage, as here depicted almost as diagnostic of Albright's syndrome as osteitis fibrosa itself (× 100).

Fig. 11 (case 5).—Lesions of osteitis fibrosa involving (*a*) ribs and scapula on left and (*b*) middle portion of sternum with expansile type of lesion.

Fig. 12 (case 5).—Lesions of osteitis fibrosa involving (*a*) first metacarpal bone and entire radius on the left and (*b*) entire left humerus. Zones of involvement predominantly left-sided. Complete skeletal involvement shown in figure 13.

and ninth thoracic vertebrae with compression fractures and destruction of the pedicles. There were similar cystic changes in the second lumbar vertebra and in the wing of the sacrum on the right side (fig. 13). What appeared at first to be a calculus in the left kidney proved on further investigation to be a large cystic defect involving the posterior portion of the twelfth rib on the left. Because the lesions were predominantly unilateral the roentgenologists suggested that they were probably not the result of hyperparathyroidism. The bones, other than those previously

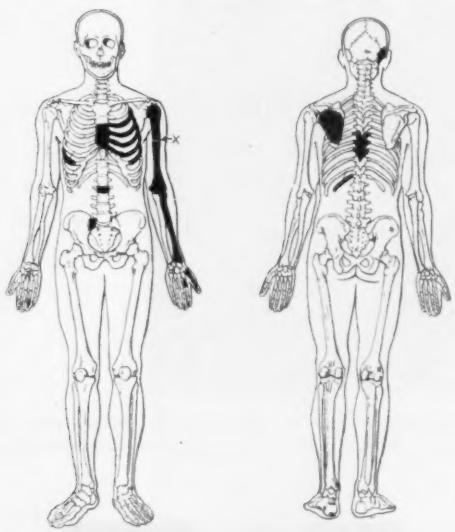

Fig. 13 (case 5).—Zones of fibrocystic involvement of bones (black areas). Posterior view shows scapular and vertebral lesions. Site of pathologic fracture is indicated by "×."

mentioned, were roentgenoscopically normal. They suggested a diagnosis of polyostotic fibrocystic disease but were unable to rule out the possibility of myeloma.

On exploration of the left humerus on July 7, a small cyst was encountered after a thin shell of cortical bone was unroofed. A thick yellowish membrane was in apposition with the bone and surrounded a cavity filled with serous fluid. The medullary cavity was greatly expanded. Microscopic examination of a piece of the wall of the cyst and bacteriologic studies of some of the fluid revealed nothing of significance. On July 16 a small specimen was removed for biopsy from one of the pigmented areas over the sacral region. The patient was dismissed on the same day. When he was last heard from in 1941, he was still having trouble with recurrent fractures.

The pathologic material in this case consisted of a few small fragments of tissue from the capsule of the humeral cyst and tissue removed for biopsy from the skin in the area of pigmentation. Both specimens had been fixed in formaldehyde solutions (10 per cent of the U. S. P. concentration). Sections prepared from the wall of the cyst revealed the picture of osteitis fibrosa with masses of fibroblastic cells loosely or compactly arranged in a rather avascular tissue. There were a few spicules of degenerating bone but practically no osteoid tissue. Giant cells were few and widely dispersed, and foam cells were absent. Numerous red blood cells were present, and the tissue was impregnated with granules of hemosiderin. Sections made from the cutaneous lesion microscopically resembled those described in the literature on Albright's syndrome and presented the appearance of pronounced hyperpigmentation of the basal layers of the stratum granulosum (fig. 14). There were no nevus cells or evidences of neurofibromas within the dermis.

Comment.—In this case of Albright's syndrome occurring in a male, progressive lesions of the bones developed relatively late, were predominantly on the left side and involved chiefly the upper portions of the skeleton. A somewhat short stature naturally raised the question of possible precocious development with early arrest of somatic growth. The presence of the pigmented spots completed the syndrome.

Fig. 14 (case 5).—Section of skin from pigmented area. The features of hyperpigmentation of the basal layers duplicate that illustrated in figure 3*b* (× 165).

Case 6.—A white boy 10 years of age was brought to the clinic on Feb. 13, 1941, for consideration of "bone trouble" which had been present for three years. The family history was not significant, and early development had been normal. No sequelae had resulted from such childhood diseases as whooping cough, measles and chickenpox. When the patient was 7 years of age, the parents noted that he walked with a limp in the left leg. Medical advice was sought, and a diet rich in vitamins and minerals was recommended. Roentgenograms at that time were interpreted as revealing polyostotic fibrous dysplasia, a diagnosis which was confirmed by biopsy of a fragment of bone from the left hip and of a lesion involving one of the ribs on the right side. The values for serum calcium, phosphorus and phosphatase were approximately normal. Clinically and roentgenologically the condition seemed to progress rather than to improve. By May 1939, the patient was forced to use crutches, and later a brace became necessary. In September 1939, a fracture through the upper portion of the right femur was

sustained, but this healed as a result of immobilization of the leg in a cast. For eighteen months progressive deformity involving the left hip in the region of the fracture had been noticed.

Physical examination at the clinic revealed a somewhat undernourished child of about the stated age. His height was 4 feet, 8 inches (142 cm.), and his weight was 67 pounds (30 Kg.). There was a bulging deformity of the left leg over the region of the greater trochanter, with coxa vara. The left leg was 1.5 inches (3.8 cm.) shorter than the right. No tenderness or limitation of motion was apparent. The only other significant physical feature was the presence of several large areas of pigmentation on the patient's back.

The values for serum calcium and serum phosphorus were, respectively, 10.1 and 3.6 mg. per hundred cubic centimeters, and the activity of the serum phosphatase

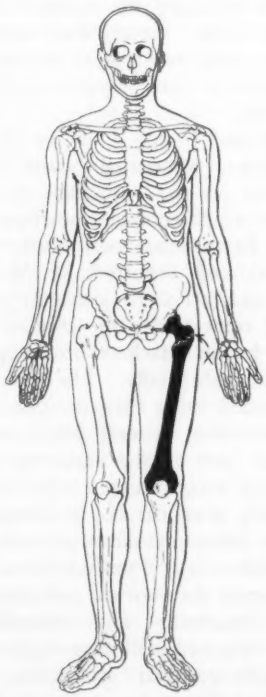

Fig. 15 (case 6).—Zones of fibrocystic involvement of bones (black areas). Site of pathologic fracture is indicated by "X."

was recorded as of 6 Bodansky units. Roentgenologic examination, limited by request to the left femoral lesions, revealed fibrocystic disease involving the entire shaft (fig. 15), an old intertrochanteric fracture and pronounced coxa vara.

Inasmuch as this patient was brought to the clinic solely for confirmation of the previous diagnosis of polyostotic fibrous dysplasia and for advice regarding the advisability of bone graft, a complete work-up was impossible. It was the consensus that a heterogenous graft carried across the zone of fracture would correct the deformity and effect a strong bony union.

Comment.—Admittedly, from the standpoint of material available for study, this case leaves much to be desired. However, the history was that of osseous lesions beginning in childhood, progressive in nature and complicated by the occurrence of a pathologic fracture. The fracture was demonstrated roentgenologically to have occurred through a fibrocystic portion. Pathologic verification of oseitis fibrosa had been obtained not only from the left femoral lesion but also from a similar lesion of a rib on the opposite side of the body. In view of the rather limited extent of the fibrocystic disease and the extensive cutaneous pigmentation, this case possibly represents another rather unusual example of Albright's syndrome.

ETIOLOGY

Although the cause of Albright's syndrome is a mystery, many investigators believe that the condition is the result of complex congenital errors in development.

Albright, impressed by the widespread distribution of lesions involving simultaneously the skin, bones and endocrine glands, postulated a primary disturbance of the central nervous system, possibly in the region of the hypothalamus. On this basis the endocrine manifestations were interpreted as arising from a disturbance of afferent impulses traveling to the pituitary body. The presence of mental disturbances in 1 of Albright's original cases served to strengthen his conviction concerning this hypothesis. Other positive neurologic signs have been recorded in several cases in the literature, and in case 1 of our series the presence of a positive Babinski sign bilaterally might support this hypothesis of a primary disturbance of the central nervous system. Even the sexual changes might occur as a result of lesions involving the central nervous system, as evidenced by the fact that these changes may follow encephalitis, poliomyelitis and even glioma, especially when the tumor is located in the region of the third ventricle and the hypothalamus. While it is perhaps noteworthy that in several cases of Albright's syndrome reported in the literature the patients had previously had encephalitis,[14] the evidence is by no means conclusive that encephalitis plays an etiologic role in the production of a disease considered by some investigators as beginning at, or even before, birth.

Possible evidence for a hereditary basis was presented in a case of polyostotic fibrous dysplasia studied by Moehlig and Schreiber. On the maternal side of the patient's family, shortness of stature and unusually early dental decay were interpreted as attributable to a hereditary defect in the bone-forming mesenchyma. Even if we could agree with this premise, we could

not understand how, as they suggested, the unilateral distribution of the osseous lesions of their patient represented a chromosomal aberration for which the maternal side of the family could be blamed. In a search of the literature the only other evidence for a familial trait in polyostotic fibrous dysplasia appeared in a report by Hirsch [15] of 3 siblings who all suffered from the effects of disseminated cystic lesions of bone.

In 2 cases of Albright's syndrome recorded by Braid,[16] a history of neonatal jaundice suggested that disturbances in hepatic function were responsible for the syndrome. Braid obtained definite evidence, based on laboratory data, of diminished liver function in 1 of her cases. She correlated an increase in the value for serum phosphatase with an inability on the part of the liver to destroy this substance, noting that in certain cases of hepatic cirrhosis similar high levels of serum phosphatase are obtained. The cases of McCune and Bruch [17] and of Summerfeldt and Brown [18] were similar in many respects to those of Braid, and it is perhaps significant that 1 of our patients (case 3) stated that she "almost died of liver trouble in infancy." At necropsy in the case of McCune and Bruch the liver was found to have a normal microscopic appearance. Consequently a primary hepatic lesion probably could not be held responsible for the bony lesions of Albright's disease, to say nothing of the apparently unrelated sexual disturbances and the cutaneous pigmentation.

A primary hormonal imbalance has been postulated on the basis of those cases in which sexual aberrations were especially prominent. However, it is difficult, as Albright remarked, to comprehend how estrogen acting independently or through the medium of the parathyroid glands [19] could explain the bizzare character and predominantly unilateral distribution of the osseous and cutaneous lesions seen in this disease. Both estrogen and parathyroid extract have produced cystic changes of bone in animals,[19] but none of these experiments has resulted in effects which combine the dissociated phenomena of Albright's syndrome.

Helfet, in an attempt to establish the nature of the osseous lesions, revived a theory that is interesting not only from the standpoint of etiology but also as a basis for therapy. He believed that there existed in Albright's syndrome a state of chronic hyperparathyroidism based on a mild hyperphosphatemia. His treatment consisted of reducing the amount of available phosphorus by precipitating part of it in the intestine by using the acetates and gluconates of aluminum. He reported some striking results after using this type of therapy for several patients who had polyostotic fibrous dysplasia of bone.

Sternberg and Joseph,[20] in one of the more recent reviews, presented some interesting etiologic data on the only case of Albright's syndrome in which complete necropsy had been performed. In this case, which previously had been studied and reported by McCune and Bruch, the patient, a 13 year old girl, subsequently had come under the care of Sternberg and Joseph for an attack of bronchopneumonia, which terminated fatally. The essential positive observations other than the osseous lesions, which are described in some detail, were limited for the most part to the endocrine glands, in which the following changes were noted: The pituitary body demonstrated pronounced hyperplasia of the basophilic elements with adenomas of microscopic size. The individual basophilic cells were larger than normal and decidedly pleomorphic. Binucleated and trinucleated giant forms were observed, with loss of granular structure. Colloid granular cytoplasm, present in certain of the cells, gave an appearance strikingly similar to "Crooke's change." [21] The picture was interpreted as evidence of greatly disturbed function. The thyroid gland presented the microscopic picture of pronounced hyperplasia but contained numerous fetal adenomas, which Sternberg and Joseph interpreted as localized involution in a chronically toxic gland. This pa-

15. Hirsch, S.: Is Generalized Osteitis Fibrosa (Paget and von Recklinghausen) Congenital? Am. J. Surg. **3**:167-175 (Aug.) 1927.

16. Braid, F.: Osseous Dystrophy Following Icterus Gravis Neonatorum: Generalized Osteitis Fibrosa with Areas of Pigmentation of the Skin and Precocious Puberty in the Female, Arch. Dis. Childhood **14**:181-202 (Sept.) 1939.

17. (*a*) McCune, D. J.: Osteitis Fibrosa Cystica: The Case of a Nine Year Old Girl Who Also Exhibits Precocious Puberty, Multiple Pigmentation of the Skin and Hyperthyroidism, Am. J. Dis. Child. **52**:743-747 (Sept.) 1936. (*b*) McCune, D. J., and Bruch, H.: Osteodystrophia Fibrosa: Report of a Case in Which the Condition Was Combined with Precocious Puberty, Pathologic Pigmentation of the Skin and Hyperthyroidism, with a Review of the Literature, ibid. **54**: 806-848 (Oct.) 1937.

18. Summerfeldt, P., and Brown, A.: Osteodystrophia Fibrosa, Am. J. Dis. Child. **57**:90-101 (Jan.) 1939.

19. Bremer, J. L.: Osteitis Fibrosa Localisata: An Experimental Study, Arch. Path. **32**:200-210 (Aug.) 1941.

20. Sternberg, W. H., and Joseph, V.: Osteodystrophia Fibrosa Combined with Precocious Puberty and Exophthalmic Goiter: Pathologic Report of a Case, Am. J. Dis. Child. **63**:748-783 (April) 1942.

21. Crooke, A. C.: A Change in the Basophil Cells of the Pituitary Gland Common to Conditions Which Exhibit the Syndrome Attributed to Basophil Adenoma, J. Path. & Bact. **61**:339-349 (Sept.) 1935.

tient had a long history of toxic diffuse (exophthalmic) goiter, and the basal metabolic rate had ranged up to plus 120 per cent. The thymus and the lymph nodes showed considerable hyperplasia. Atrophy of the adrenal cortex contrasted with relative hypertrophy of the medullary tissue. Ovarian tissue resembled that of an adult woman, with multiple follicular cysts but with an absence of mature or maturing corpora lutea. Sternberg and Joseph contrasted this observation with the condition present in cases of adrenal cortical hyperplasia and tumor, in which the ovaries are often hyperplastic. Parathyroid glands were all identified and were essentially normal in appearance. Of particular interest was the authors' observation that the liver was normal, in spite of the history of severe neonatal jaundice. It is perhaps also noteworthy that no lesions of the brain, except a slightly dilated third ventricle, were demonstrated on either macroscopic or microscopic examinations and that no abnormality was evident on careful study of the hypothalamus.

Sternberg and Joseph found it impossible to accept the theory of causation based on the principle of multiple congenital defects of development even though, in addition to the manifestations of Albright's syndrome in its most florid form, their patient had had a patent foramen ovale and Meckel's diverticulum. It was their considered opinion that the osseous changes, cutaneous pigmentation and precocious puberty were on an endocrine basis and that in their case the etiologic importance of thyrotoxicosis was paramount. In the bizarre distribution of the osseous and cutaneous lesions they saw a "localized tissue susceptibility" paralleled by recorded instances of hemihypertrophy, hemiobesity, unilateral exophthalmos and so forth.

Several other cases of Albright's syndrome have been recorded in which clinical evidence of thyrotoxicosis was manifest, but in 1 of these biopsy of the thyroid gland revealed normal colloid thyroid. Moreover, the large majority of patients in the recorded cases did not have hyperthyroidism. Consequently the case of Sternberg and Joseph may fall into a special category. The changes they depicted as involving the basophilic elements in the pituitary body were as arresting as those in the thyroid gland, and perhaps some investigators would be inclined to feel that the endocrine manifestations had occurred as a result of a primary disorder involving the pituitary gland.

SYMPTOMS AND SIGNS

Next to the sypmptoms of precocious puberty in females, the osseous lesions that characterize Albright's syndrome provide the cardinal clinical symptoms. Limitation of movement that results from bony deformity and pathologic fractures are often childhood manifestations. However, in cases 1 and 5 of our series extensive bony lesions had been practically unnoticed until the patients were well on in adult life. Generalized "bone pains," so characteristic of hyperparathyroidism, are usually absent in uncomplicated cases, but local pain and tenderness may be present if the involved bone is the site of an expanding fibrous tumor and are naturally present when a pathologic fracture has occurred. Strangely enough, these fractures tend to heal after the use of standard methods of immobilization or surgical fixation by means of grafts [22] or both.

Lichtenstein and Jaffe were of the opinion that the osseous lesions constitute the nucleus of the disorder and felt that other clinical manifestations, such as precocious puberty and cutaneous pigmentation, can occur only in the presence of extensive skeletal involvement. Cases 2, 5 and 6 of our series provided notable exceptions to this general rule. Although precocious puberty is a cardinal symptom of Albright's syndrome in the complete form, it is almost exclusively limited to females and usually to those females in whom extensive osseous lesions are also present. However, there are exceptions to this rule, of which case 1 is an example. The reason for precocious puberty is poorly understood, but its implications are often far reaching, for in addition to the early onset of menstruation and the early apearance of secondary sexual characteristics there is sometimes pronounced acceleration in somatic maturation. Thus the bone age may exceed the chronologic age of the patient, in that there is premature ripening of the epiphyses. In addition, epiphyses unite early with diaphyses, and, in the case of bones of the extremities, the result may be a premature arrest of growth. It has accordingly been observed that adult females who suffer from the disease are of short stature.

INCIDENCE

Albright's syndrome is somewhat rare if one considers only the complete form, as exemplified by the cases listed in table 1 and, in addition, the occasional case which may have escaped our notice in a review of the literature. However, other authors, such as Gorham and co-workers, consider the incomplete form, in which one or more of the clinical, roentgenologic and pathologic features are lacking, and thus remove the condition somewhat further from the realm of

22. Ghormley, R. K.; Sutherland, C. G., and Pollock, G. A.: Pathologic Fractures, J. A. M. A. **109**:2111-2115 (Dec. 25) 1937.

the uncommon. Furthermore, if one agrees with Lichtenstein and Jaffe that polyostotic fibrous dysplasia in its most florid expression demonstrates the extraskeletal manifestations of Albright's syndrome, an extensive literature is available. Jaffe, to cite one investigator, has had personal experience with at least 23 cases, and Albright has encountered approximately 30.

In the matter of sex, females predominate over males in the ratio of 3 to 2. It is interesting to note that this same ratio obtains for the sex incidence among patients suffering from the effects of parathyroid adenoma. No racial susceptibility to the disease has been emphasized in the literature.

It has been suggested in the literature that increased fertility may be a feature of Albright's syndrome in females. Moreover, it has been asserted that in the case of Lena Medina, the 5 year old Peruvian girl who gave birth to a boy, precocious puberty was attributable to this condition. However, a letter which one of us (M. B. D.) received from Albright,[23] who had corresponded with one of the physicians in charge of the case, did not confirm this theory.

Extensive cutaneous pigmentation, often occurring in the form of large irregular patches, is an almost constant accompaniment of osseous lesions of pronounced degree in Albright's syndrome. Strangely, these patches of pigmentation may occur with a predilection for the side of the body that has the most pronounced bony lesions. The locations of the pigmented spots vary, but the back, buttocks, inner aspects of the thighs, neck and scalp are common sites. In case 4 of our series, a large pigmented spot on the occipital portion of the scalp was the only discolored area of the skin and was associated with alopecia of this same region. Similar localization of pigmentation of the scalp has been observed by others.

OTHER OBSERVATIONS

Laboratory Data.—The results of chemical analysis of blood, urine and feces of patients who have Albright's syndrome are usually as follows: Values for serum calcium and serum phosphorus are variable but usually are within the limits of normal. Serum phosphatase is increased, the amount of increase being in general consonant with the degree of activity of the osseous lesions. Studies on calcium balance have varied; in some cases equilibrium has been noted, in some cases a measurable degree of retention and in others a state of so-called negative balance. Excessive excretion of calcium ordinarily is interpreted as favoring a diagnosis of parathyroid tumor, but in at least 1 case reported in the literature it was associated with polyostotic fibrous dysplasia. Consequently it is doubtful whether the results of calcium studies alone can be the deciding factor in the differential diagnosis of this condition from hyperparathyroidism resulting from hyperplasia or tumor. High values for serum cholesterol occasionally have been reported and have resulted in the mistaken diagnosis of xanthoma of bone. In practically all cases of Albright's syndrome the values for serum cholesterol have been normal. In a few cases of this disease such diversified observations have been reported as decreased dextrose tolerance with or without glycosuria, diminished hepatic function as evidenced by retention of dye, abnormal values for serum protein, elevation of the basal metabolic rate and increased urinary excretion of estrogen. In the majority of cases, however, such evidence has not been obtained, and its seeming importance diminishes when one attempts to apply it generally in the study of Albright's syndrome.

Roentgenologic Characteristics.—As a rule, polyostotic fibrous dysplasia has a distinctive roentgenologic appearance, and in most instances the correct roentgenologic diagnosis can be made without difficulty. In most cases several or many bones are affected, but in some cases only one bone or part of a bone is involved. The solitary lesions of bone most frequently cause difficulty in diagnosis. When Albright's syndrome is present, involvement of many bones almost always occurs. Osseous lesions of polyostotic fibrous dysplasia sometimes are limited strictly to one side of the body; but when there is extensive skeletal involvement, the lesions are often bilateral, most of the lesions being on one side. The lower extremities are involved more frequently than the upper extremities. The skull frequently is affected. The lesions are disseminated, and normal bone is present between the regions of abnormal bone. Polyostotic fibrous dysplasia almost always can be distinguished from hyperparathyroidism, because in the latter there is generalized abnormality of bone. The epiphyses are not affected by polyostotic fibrous dysplasia, which is an important consideration in distinguishing this condition from Ollier's disease (dyschondroplasia).

Lesions of polyostotic fibrous dysplasia consist mainly of masses of fibrous tissue which in most instances replace the medullary structures of the involved bone. This leads to thinning of the cortex of the bone from within, and in many cases there is moderate or extreme expansion of the involved bone. These changes result in a distinctive roentgenologic appearance, such as

23. Albright, F.: Personal communication to the authors.

was observed in case 5 (figs. 11 and 12). It must be emphasized, however, that at times the lesions of polyostotic fibrous dysplasia may develop subperiosteally, as illustrated by case 4 (fig. 9), and thereby cause erosion of the cortex from without. In cases of this type, slight or no expansion of involved bone occurs, and the roentgenologic appearance is considerably different from that of lesions beginning in the medullary portion.

Since in polyostotic fibrous dysplasia the bony structures are replaced by masses of fibrous tissue, the involved portions of bone are abnormally radiolucent. For this reason focal involvement that starts in the medulla and causes expansion of bone may resemble cystic lesions of bone. Localized zones of osteosclerosis frequently are found in association with radiolucent lesions, and in some cases osteosclerosis is most conspicuous.

Bones affected by polyostotic fibrous dysplasia are sometimes abnormally long. When Albright's syndrome is present the growth of bone may be accelerated during childhood, but premature union of the epiphyses may cause an early arrest of growth and resulting dwarfism. When adult life has been reached the lesions of bone no longer progress or progress very slowly.

Pathologic fractures which frequently complicate this condition usually occur through regions of major involvement. Periosteal reaction develops if a pathologic fracture is present; otherwise no periosteal reaction is produced by these lesions. Pathologic fractures often result in shortening and gross deformity of bone. When there is extreme involvement of a bone, multiple fractures may produce a peculiar crumpled appearance. The rapid healing of pathologic fractures indicates that the reparative process proceeds in an orderly fashion.

Lesions of the skull frequently are seen in polyostotic fibrous dysplasia. The changes in the vault, occiput and mandible closely resemble those that occur elsewhere in the skeleton. Frequently expansion of these parts of the skull occurs. Radiolucent zones resembling cysts may be present. Little, if any, osteosclerosis is present in these regions. The lesions affecting the basal portion of the frontal bone and sphenoid, ethmoid and maxillary bones are different from the lesions of fibrous dysplasia as seen elsewhere. In these locations the lesions are almost always osteomatoid in type. The bone is extremely dense and thick. Complete or partial obliteration of the paranasal sinuses frequently is present. Deformity of the orbit with ocular proptosis is not unusual. Obstruction of the nasal passages may occur. Expansion of the involved bone may result in asymmetry of the skull. Extreme prominence of the forehead, maxilla or mandible is not uncommon.

The osteomatoid thickening of the base of the skull, especially of the wings of the sphenoid bone or of the basal portion of the frontal bone, may simulate the hyperostosis that is associated with meningioma. These lesions of the skull have a superficial resemblance to those seen in Paget's disease, but distinction should not be difficult. The term leontiasis ossea is used to designate a type of generalized facial deformity. Almost always, however, this deformity is the result of polyostotic fibrous dysplasia; hence no distinction between the two conditions is necessary.

Pathologic Features.—The cortex of the involved bony segments is thinned, and the substantia spongiosa and marrow are filled with fibrous tissue, which may be vascular or avascular. Occasional spicules of degenerating and regenerating bone are found, the latter often being surrounded by normal numbers of osteoblasts. Islands of cartilaginous metaplasia occasionally are observed. Blood pigment sometimes is noted. There is a characteristic paucity of osteoclasts and those present have been described as being abnormal. In other cases, especially around sites of recent fractures, osteoblastic and osteoclastic activity may be pronounced and the picture may simulate that of benign foreign body giant cell tumors of bone. Cysts are not commonly encountered except in regions in which degenerative changes are observed. Foam cells have been described in a few cases, and we have seen them in our own specimens; however, they are usually absent, and differentiation of the condition from xanthoma of bone presents no diagnostic difficulties.

In cases of Albright's syndrome bones that appear normal roentgenographically present a normal appearance on biopsy, but in cases of hyperparathyroidism all sections reveal mild to extreme osteoporosis. Although Jaffe expressed the belief that in cases of Albright's syndrome there is fibrosis of the bone marrow which is not observed in cases of hyperparathyroidism, most investigators are willing to concede that a differential diagnosis cannot be made from biopsy of an isolated fragment of porous bone. Consequently the pathologic interpretation should be considered in conjunction with an evaluation of the clinical history, roentgenographic findings and the results of chemical analysis of the blood.

Pathologic interpretation of the cutaneous lesions has been made possible through biopsy

in a number of cases. The changes have been constant and have paralleled the observations made in 2 of our own cases. The lesion demonstrates an excess of melanin pigment, which sometimes is confined to the basal layer of the epidermis but occasionally extends into the granulosum. There may be a few melanophores in the cutis, but as a rule there are no nests of nevus cells as in the ordinary mole. An associated hypertrophy of the muscular elements comprising the arrectores pilorum recalls the precocious puberty with early appearance of axillary and pubic hair which is observed in some females who have this strange malady.

DIFFERENTIAL DIAGNOSIS

Precocious puberty, which is present in association with a florid or complete form of Albright's syndrome, is a phenomenon that is not associated with parathyroid adenoma. Consequently differential diagnosis should offer few difficulties. Nevertheless in the past the notion that porous bones indicate the presence of hyperparathyroidism has become so fixed that at least 20 patients who had complete or incomplete forms of Albright's syndrome have been submitted to fruitless explorations of the neck in search of a causative tumor. In incomplete forms of the disease, the fact should be borne in mind that hyperparathyroidism is rare in childhood, whereas Albright's syndrome usually dates from an early age. In the former disease patients complain of pain in the bones, profound muscular weakness and digestive disturbances, whereas patients suffering from the latter appear well except for the local disability produced by severe osseous lesions. Generalized pain in the bones is not often encountered. In cases of hyperparathyroidism widespread osteoporosis is present, whereas in Albright's syndrome the osseous lesions are spotty in character and often unilateral in distribution, with roentgenologically normal bone in many regions. Cysts are the exception rather than the rule. Renal lithiasis and fixation of the specific gravity of urine, so commonly found with parathyroid adenomas, are rarely observed with Albright's syndrome.

The high values for serum calcium, low values for serum phosphorus and noticeably negative calcium balance in cases of hyperparathyroidism contrast with the normal values obtained in cases of Albright's syndrome. High values for serum phosphatase may be obtained in both conditions. A pronounced increase in the excretion of calcium as compared with the intake (negative calcium balance) favors a diagnosis of hyperparathyroidism, but one occasionally encounters a case which proves an exception to this general rule.

The differentiation of Ollier's dyschondroplasia from Albright's syndrome may give rise to some diagnostic difficulties, inasmuch as it too occurs in young persons. The finding of occasional islands of cartilage in the bony lesions of Albright's syndrome heightens this similarity. However, Ollier's disease is a disturbance of chondrification and therefore does not involve bones that are laid down in membrane, such as those of the skull. Moreover, disturbances of the epiphyses are characteristic of Ollier's disease, whereas absence of involvement of epiphyses is a noteworthy feature of Albright's syndrome. Cutaneous pigmentation in both sexes and precocious puberty in females are additional differentiating features of Albright's syndrome.

Osteogenesis imperfecta often presents blue sclera and sometimes certain other hereditary evidences which appear to be of value in differential diagnosis. Blue scleras occasionally have been reported in association with polyostotic fibrous dysplasia.[24]

Von Recklinghausen's neurofibromatosis, with its characteristic pigmentation of the skin, also may be associated with osseous lesions and thus complicate the problem of differential diagnosis. The presence of neurofibromas along the course of cutaneous nerves provides an important clue, and the diagnosis easily can be settled by biopsy. Neurofibromas do not occur in connection with Albright's syndrome.

In locations other than the vertebral bodies, hemangiomas of bone may have certain features in common with polyostotic fibrous dysplasia.[25] The value of biopsy in such cases is again obvious. The gross appearance of the two lesions, however, is entirely different.

According to the early literature, xanthomatosis presented problems of differential diagnosis, and several cases of Albright's syndrome have been recorded as typical examples of xanthoma of bone. Involvement of the cranium in cases of Albright's syndrome in young persons may simulate that found in xanthomatosis. Clinical studies on the level of cholesterol and other lipids of the blood may establish the diagnosis in an occasional case. In others biopsy of an osseous lesion will be necessary. Foam cells occasionally are encountered in the bony lesions associated with Albright's syndrome but never

24. Nichols, B. H.: Fragilitas Osseum; Brittle Bones and Blue Sclera; Hereditary Mesenchyme Hypoplasia, Cleveland Clin. Quart. **7**:58-65 (Jan.) 1940.

25. Pierson, J. W.; Farber, G., and Howard, J. E.: Multiple Hemangiomas of Bone, Probably Congenital, J. A. M. A. **116**:1245-1248 (May 10) 1941.

in the abundance in which they may be present in xanthoma.

Biopsy also may be necessary to rule out a diagnosis of metastatic cancer, which was first considered in case 2 of our series. A similar procedure theoretically might be adopted in cases of so-called latent lesions that might be mistaken roentgenologically for certain primary malignant tumors of bone, such as multiple myelomas.

Granulosa cell tumor of the ovary produces precocious puberty but usually none of the other features of Albright's syndrome. Adrenal tumors may be recognized by the fact that those producing precocious puberty (cortical) rarely metastasize to bone and those metastasizing to bone (medullary) do not produce precocious puberty.

TREATMENT

In general, no specific treatment for Albright's syndrome has been developed. In the cases with extensive osseous involvement the most promising results have followed the use of aluminum acetate as recommended by Helfet. Both clinical and roentgenologic improvement have been noted after the use of this preparation in cases of osteoporosis. Our experience has not been extensive enough to warrant the claim that anything approaching a cure can be obtained by the use of aluminum acetate, nor do we know how long the improvement might be sustained.

Treatment with vitamin D and calcium in various forms seems to have produced little or no beneficial effect. Roentgen therapy has been tried from time to time. While in a localized lesion it may produce some sclerosis and fibrosis, its use is contraindicated when the condition is more generalized. In children, extensive irradiation over epiphyses is likely to lead to arrest of epiphysial growth.

Pathologic fractures should be reduced and splinted in a manner similar to that of any other fracture, and early union usually results. In cases of pathologic fracture in which large cysts occur, restoration of the bony substance and healing of the fracture can be hastened by a bone grafting procedure.

In all cases of Albright's syndrome, whether treated by medical or surgical means, we believe that the use of aluminum acetate with at least one pint of milk a day is indicated.

SUMMARY AND CONCLUSIONS

Six new cases of Albright's syndrome were encountered at the Mayo Clinic. These bring the cases reported in the literature to a total of 39. Information concerning these cases and 1 reported by Shallard has been added to the tabulated review of the literature prepared by Gorham and co-workers in 1942.

The disease occurs more commonly among females than among males and frequently manifests itself early in childhood. Several of our patients were found to have latent lesions in adult life.

In some females who have Albright's syndrome, sexual and somatic development are precocious. In males there may be some evidence of somatic precocity but few sexual changes. In both sexes, but particularly among females, premature arrest of growth may occur. Cutaneous pigmentation accompanies the disease in both males and females.

Extraskeletal manifestations may occur in the absence of extensive osseous lesions. This observation is contrary to the general impression obtained from the literature. Clinically silent but roentgenologically extensive and active lesions of bone can be present in adults who have Albright's disease. This observation also differs from those recorded in the literature. A tendency in our cases toward unilateral involvement of bones was in harmony with the findings of other investigators. The osseous lesions appeared to be responsible for the major complications of the disease. Symptoms so produced were in general progressive in severity, but remissions and exacerbations, with sometimes long periods of clinical quiescence, were observed.

Pathologically the picture was that of a profound disturbance of metabolism of bone in which decalcification and resorption equaled or exceeded the processes of tissue repair by osteoblasts and fibroblasts. Contrary to previous observations, microscopic examination in our cases occasionally demonstrated brown tumors and cysts. The microscopic resemblance to giant cell tumor in some of our material was also unusual. Accordingly, we agree with those investigators who claim that the diagnosis of Albright's syndrome cannot be made solely on the basis of microscopic studies.

In our series we were unable to see how hepatic disease or thyrotoxicosis played any part in causing this condition. Evidence of a lesion involving the central nervous system was in 1 case equivocal.

Whether chronic hyperphosphatemia existed in these 6 cases is uncertain, but therapy based on this assumption was applied with some success in 1 case. If the results in additional cases are promising, the method should prove of benefit to persons affected with this strange malady.

INFECTIOUS MONONUCLEOSIS

AN ANALYSIS OF THREE HUNDRED CASES WITH THREE CHARACTERIZED BY RARE HEMATOLOGIC FEATURES

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The variegated clinical manifestations of infectious mononucleosis have been emphasized repeatedly by most writers on the subject in recent years.[1] It has also been emphasized that these manifold signs and symptoms often make the diagnosis difficult, because frequently some particular combination of symptoms of the disease will duplicate the important findings of other clinical entities.

We have reviewed a series of 300 cases of infectious mononucleosis observed over the past twenty months at several large air force hospitals, and we also have encountered the same long list of heterogeneous symptoms and signs that have been observed and recorded by other investigators. Moreover, we find that the relative frequency of these manifestations, with but insignificant percentage variations, closely approximates that observed by previous authors. In addition, however, to these manifestations, we have observed in this series 3 cases characterized by a severe anemia with leukopenia and thrombopenia which presented considerable difficulty in diagnosis. Therefore, it was thought worth while to review briefly this rather large series of cases, recording the symptoms and signs, and further to give a more detailed discussion of the 3 cases with the characteristics just referred to.

In this series of 300 cases the complaints of the patients when they were admitted to the hospital were not so variable as the diagnoses made on admission. Tables 1 and 2 illustrate this point.

From the tables it will be noted that the most frequent complaints were sore throat, enlarged lymph nodes, headache and fever. Furthermore, in only 37 cases in the entire series was the disease correctly diagnosed on the patient's admission to the hospital.

TABLE 1.—*Admission Diagnoses*

Diagnosis	Cases
Acute pharyngitis	64
Nasopharyngitis	45
Infectious mononucleosis	37
Acute tonsillitis	36
Atypical pneumonia	19
Acute sinusitis	12
Diagnosis uncertain *	12
Lymphadenitis	10
Bronchitis	10
Malaria	7
Jaundice	6
Cervical myositis	5
Vincent's angina	5
Influenza	4
Epistaxis	4
Gastroenteritis	3
Suspected meningitis	3
Cervical mass	2
Heat exhaustion	2
Reaction to typhoid vaccine	1
Psychoneurosis	1

* These patients were admitted to the hospital for observation.

TABLE 2.—*Admission Complaints*

Complaint	Cases
Sore throat	146
Lymphadenopathy	81
Malaise	72
Headache	71
Fever	67
Anorexia	58
Cough	38
Abdominal pain	14
Cutaneous eruption	11
Nausea	9
Vertigo	9
Vomiting	7
Arthralgia	7
Jaundice	6
Epistaxis	6
Myalgia	5

Many writers have divided infectious mononucleosis into three types: namely, the anginose, the glandular and the febrile. In our series 150 cases were instances of the anginose, 127 of the glandular and 23 of the febrile type.

1. Tidy, H. L.: Glandular Fever and Infectious Mononucleosis, Lancet **2**:180 and 236, 1934. Spark, T. E. H.: Infectious Mononucleosis: Problem in Diagnosis, M. J. Australia **2**:413 1942. Werlin, S. J.; Dolgopol, V. B., and Stern, M. E.: Infectious Mononucleosis, a Diagnostic Problem, Am. J. M. Sc. **201**: 474, 1941.

In all 300 of these cases there was a positive heterophile agglutination in dilutions ranging from 1 to 112 to 1 to more than 10,000.

The list of different conditions observed in this series serves to stress the often repeated statement that infectious mononucleosis is a disease of remarkable variablity. Table 3 serves to illustrate this point.

The table shows that in 172 cases of this series a generalized adenopathy was observed and in 123 enlarged cervical nodes only were seen. In 67 cases the enlarged nodes were tender. The spleen was palpable in 104 cases and the liver in 47. In 9 cases the patients had generalized petechiae, and in 4 petechiae were found in the oral cavity. In 16 cases

TABLE 3.—*Positive Signs*

Generalized adenopathy	172
Cervical adenopathy only	123
Follicular pharyngitis	112
Palpable spleen	104
Tender adenopathy	67
Palpable liver	47
Tender spleen	39
Gingivitis	37
Membranous pharyngitis	34
Acute tonsillitis	29
Dermatitis	16
Jaundice	11
On admission	6
Petechiae	9
Oral cavity	4
Generalized	9
Nausea	9
Peritonsillar abscess	7
Vomiting	7
Epistaxis	6
Myositis	5
Diarrhea	4
Hemoptysis	3
Abdominal tenderness	3
Mild stupor	3
Stiff neck	2
Delirium	1

dermatitis which was usually either scarlatinal or macular was noted. In 3 cases the patients had hemoptysis; in 11 they were jaundiced, and in 6 of the latter they were jaundiced on admission. Mild stupor, stiff neck and even delirium were observed in rare instances.

The symptoms and signs seem to fall roughly into four main groups: (1) respiratory, characterized by nasal obstruction, cough, epistaxis, pharyngitis and tonsillitis; (2) gastrointestinal, by nausea, vomiting and abdominal tenderness; (3) hematologic, by hypoplastic and hemolytic anemia as well as thrombopenia and leukopenic neutropenia, and (4) dermatologic, by scarlatinal or macular rashes as well as pruritus with and without jaundice.

A recent report of a case by Ziegler,[2] recording the observations at necropsy in a case of infectious mononucleosis in which rupture of the spleen was the cause of death, sheds considerable light on the pathogenesis of this disease. Moreover, the histologic observations in Ziegler's case may explain the wide variety of signs and symptoms in infectious mononucleosis. Ziegler found focal interstitial infiltrates in the liver and kidneys with proliferation of reticulum cells and necrosis, and it was his opinion that these lesions probably represented "an acute infectious granulomatous process." Furthermore, he observed pulmonary lesions in which there was distention and often obstruction of the alveolar capillaries with mononuclear cells, together with scattered perivascular and interstitial mononuclear infiltrates.

These observations suggest that infectious mononucleosis is an infection which may localize in many tissues and organs.

Since the principal objective of this paper is to discuss the cases with certain rare hematologic features, we will review them briefly. In this entire series of 300 cases there were 6 which were distinguished by moderate to moderately severe anemia. Anemia has always been considered a rare manifestation of infectious mononucleosis and usually has been thought to be due to some complicating factor unrelated to the primary disease. Unfortunately, complete clinical and laboratory studies with thrombocyte counts were carried out in only 3 of the 6 cases in this series.

REPORT OF CASES

CASE 1.—A 30 year old white woman entered the hospital because of severe occipital headaches, malaise and loss of appetite.

She was in good health until two weeks prior to her admission, when she noticed that it was becoming difficult to do her daily work. For three days prior to admission she had awakened each morning with a severe occipital headache which grew worse as the day proceeded. A blood count done a week before her admission showed no abnormality.

The past history revealed nothing significant. She had had the usual childhood diseases but no serious illness or operations.

Physical examination showed a well developed woman in no acute distress. There was a fine macular rash on the left side of her face extending from the ear over the left cheek to the side of the mouth; the rash did not fade on pressure. Small discrete nontender cervical lymph nodes were palpable bilaterally. The tip of the spleen was barely palpable.

The blood pressure was 126 systolic and 75 diastolic. The pulse rate was 90, the temperature 100 F. and the respiratory rate normal.

Roentgenologic examination revealed that the chest was normal.

2. Ziegler, E. E.: Infectious Mononucleosis: Report of a Fatal Case with Autopsy, Arch. Path. **37**:196 (March) 1944.

Examination of the blood showed a red cell count of 3,680,000, a hemoglobin content of 12.2 Gm. and a white cell count of 8,400, of which 75 per cent were lymphocytes, 20 per cent segmented forms, 1 per cent stab forms, 3 per cent monocytes and 1 per cent eosinophils. Reticulocytes numbered 1.8 per cent, and platelets, 257,600. A heterophile agglutination occurred in a 1 to 792 dilution. Other laboratory results were entirely normal.

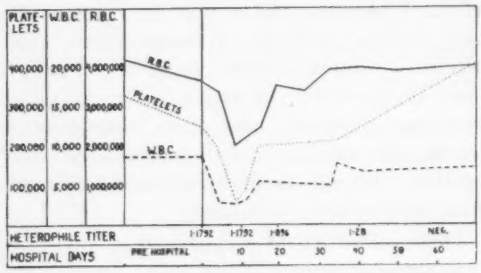

Chart 1.—Results of blood counts and heterophile agglutination tests in case 1.

The patient was given codeine, ½ grain (0.03 Gm.), for headache. No other medication was administered.

The clinical course was relatively steady, and the fatigue and malaise grew worse and did not remit until about the eighth day after the patient entered the hospital. From that day on a progressive improvement was noted.

Serial blood counts, platelet and reticulocyte counts and heterophile agglutination tests were done.

The hematologic picture in this case was one of increasing anemia, thromboperia and leukopenia which gradually returned to normal, the patient being discharged on the nineteenth day in the hospital.

CASE 2.—The patient, an active, healthy, 19 year old white youth undergoing training as an aerial navigator, was first seen three days prior to his admission to the hospital, complaining of coryza, sore throat and malaise.

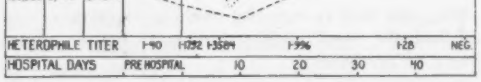

Chart 2.—Results of blood counts and heterophile agglutination tests in case 2.

At this time physical examination revealed an injected pharynx but otherwise nothing abnormal. A blood count was done, with entirely normal results. On the day of his admission the patient became acutely ill with nausea, vomiting and an extremely sore throat. Examination then revealed generalized small nontender lymph nodes. The spleen and liver were not palpable. A macular rash was noted over the chest and upper part of the abdomen. Hematologic studies at this time revealed a moderate lymphocytosis, and the heterophile agglutination test elicited a positive reaction in a 1 to 56 dilution.

The patient was put at complete rest in bed and was given a liquid diet. No other therapy was instituted.

On the fourth day after he entered the hospital it was noted that he had a few petechiae over the tibial areas, the trunk and the arms. Repeated counts revealed 250,000 platelets per cubic millimeter and a heterophile agglutination reaction in a 1 to 1,792 dilution. No complaints were noted except malaise, sore throat and a stuffy nose. The spleen was barely palpable at this time.

Daily platelet counts were done, and on his seventh day in the hospital repeated counts revealed a level of 60 to 90,000. The heterophile agglutination occurred in a 1 to 3,984 + dilution. Examination revealed many petechiae over the entire body and a small hemorrhage of the conjunctiva of the left eye and clotted blood in the left nasal cavity.

Symptomatic treatment was continued, and the patient gradually returned to normal, being discharged from the hospital on the twenty-fourth hospital day.

Rechecks revealed a normal hematologic balance and no palpable nodes or spleen.

CASE 3.—A 22 year old white naval officer was admitted to the hospital, complaining of severe nausea, shortness of breath and headache. Approximately four

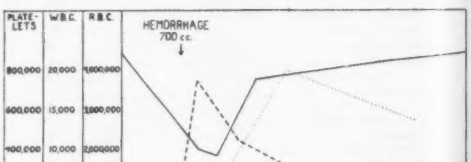

Chart 3.—Results of blood counts and heterophile agglutination tests in case 3.

hours before his admission he had been overcome by smoke from a smoke generator while he was on maneuvers.

The past history was entirely noncontributory.

Physical examination revealed a well developed white man who was acutely dyspneic. There were two minor abrasions of the scalp over the left parieto-occipital area. The respiratory rate was 32; the chest was symmetric, and expansion was equal. The patient was dyspneic but not cyanotic. The breath sounds were somewhat distant throughout. Occasional subcrepitant rales were heard throughout both pulmonary fields anterior and posterior. The heart sounds were distant, the pulse rate 140.

The patient was given oxygen inhalations and symptomatic treatment consisting of 50 per cent dextrose by vein and theophylline ethylenediamine. On his admission the blood count was normal except for a moderate lymphocytosis, the total white cell count being 4,200.

On his third day in the hospital the patient vomited approximately 700 cc. of bright red blood and clots and passed several black stools which contained occult blood. Results of examination were approximately the same as at the time of his admission, except that the spleen and liver were palpable. A blood count at this time showed 2,240,000 erythrocytes, a hemoglobin content of 7.5 Gm.

and a positive heterophile agglutination reaction in a 1 to 1,992 dilution. The patient was given 500 cc. of whole blood and 500 cc. of plasma. The count steadily declined until the eighth day, when the count revealed 1,900,000 erythrocytes, 100,000 platelets and white blood cells 18,500 with 87 per cent lymphocytes. Heterophile agglutination occurred in a 1 to 1,992 dilution. He was given 1,000 cc. of whole blood. The icteric index at this time was 31; the indirect van den Bergh reaction was 3.5.

On the tenth day a generalized macular eruption appeared on the entire abdomen and thorax.

The patient gradually improved; the hematologic picture steadily returned to normal, and the patient was discharged on the fortieth day in the hospital.

The smoke was said to contain no toxic chemical ingredients.

Platelet counts in all 3 cases were made both by the method of Dameshek and by a modified Vilariño and Pimentel technic.[2a]

COMMENT

A glance at the charts on these 3 cases shows a rapid and simultaneous drop in red blood cells, white cells and platelets, with a rapidly increasing heterophile agglutination followed by a much more gradual rise in all three of the formed blood elements and a concomitant fall in the heterophile titer.

An interesting feature of these cases is the complete lack of any of the usual clinical manifestations of infectious mononucleosis, and in cases 1 and 2 no toxic factor or other clinical finding was encountered that might account for the rapidly developing anemia, leukopenia and thrombopenia. In case 3 the only possible cause of the illness might have been the inhalation of smoke.

These 3 cases may serve to emphasize the fact that a differential diagnosis between leukemia and infectious mononucleosis cannot be made on the absence of anemia plus the presence of immature lymphocytes alone. Furthermore, the diagnosis cannot depend on the additional presence of a positive heterophile antibody agglutination, since Kent [3] has reported a case of rapidly fatal monocytic leukemia in which a high and rapidly increasing heterophile agglutination titer was present. One of us (F. C. H.) had the opportunity to study this case, and it was a classic example of leukemia with widespread heteroplastic infiltrates. Even though a positive heterophile agglutination reaction is rare except in patients with infectious mononucleosis and in patients recently treated with horse serum, it does sometimes appear in those with leukemia. Hence, the presence of abnormal though chiefly mature lymphocytes in association with a positive reaction to a Paul-Bunnell test does not, as many laboratory technicians think, clinch the diagnosis of infectious mononucleosis. Therefore, the necessity exists for careful and painstaking morphologic studies of the blood in certain bizarre cases of infectious mononucleosis.

We can only hypothesize as to the cause of this apparently rare triad of complications of infectious mononucleosis which we have just presented. It is our belief that any of these complications may occur singly. Certainly leukopenia is not at all rare. We were able to find, however, records of but few cases of proved thrombopenic purpura from infectious mononucleosis in the literature.[4] A study of Magner's case shows that no platelet counts were made and a paucity of platelets on the stained film was the only evidence of thrombopenia submitted. Anemia as a complication of infectious mononucleosis, though rarely recorded, is occasionally observed, and it is quite possible that thrombopenia might be found more frequently if in all cases in which petechiae are encountered platelet counts are performed.

The anemia has been ascribed to a hemolytic process,[5] and it has been more or less dogmatically stated that "anemia does not occur in uncomplicated cases" of infectious mononucleosis.[6] It is our belief that the anemia may also result from an infiltration of the bone marrow, with a resultant depression of all the formed blood elements. Freeman,[7] studying surgical biopsy specimens of the bone marrow in infectious mononucleosis, has apparently demonstrated such an infiltration. Moreover, it does not seem unreasonable to assume such an infiltration in view of the observations by Ziegler, in whose case visceral infiltrative lesions were encountered. Furthermore, Kilham and Steigman [8] found infiltrates similar to those of Ziegler in biopsy specimens of the liver. If such an infiltration should be the cause of the anemia, leuko-

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penia and thrombopenia in these cases that we have recorded, the lesion in the bone marrow is probably more in the nature of a focal infectious granulomatous process than a simple heteroplastic infiltration. At least this is our belief.

CONCLUSIONS

Three hundred cases of infectious mononucleosis were observed, and the usual long and varied list of clinical findings were encountered. Only cases showing a positive heterophile agglutination reaction were included in this series.

In 6 cases the patients had anemia, and in 3 of this group there were leukopenia and thrombopenia which came on rapidly. In none of these 3 cases were any of the usual clinical manifestations of infectious mononucleosis present, with the exception of mild adenopathy.

It is hypothesized that this triad of hematologic findings may have been due to depression of the activity of the bone marrow resulting from an infectious granulomatous process involving the marrow. It is further hypothesized that such a pathologic process may also be the underlying cause for the disturbances of the central nervous system and for the pulmonary, gastrointestinal and hepatic manifestations which are sometimes seen in infectious mononucleosis.

AZOTEMIA ASSOCIATED WITH GASTROINTESTINAL HEMORRHAGE

AN EXPERIMENTAL ETIOLOGIC STUDY

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Many workers [1] have confirmed the original observations of Sanguinetti [2] that an elevation of the nitrogen content of the blood may be associated with gastroenteric bleeding. Opinions concerning the pathogenesis of this condition are not in agreement. Sanguinetti [2] attributed the azotemia to absorption of protein from the intestine, augmentation of general metabolism and chloropenia. Alsted [1c] studied the condition in patients and suggested blood pressure effects and intestinal absorption as possible causes. Bookless [1s] expressed the belief that the elevated blood urea levels were mainly due to rapid breakdown of tissue protein. Black [1r] suggested and Johnson [1o] stated that azotemia does not occur in patients in the absence of reduction in renal function. The former believed the evidence inadequate to establish renal impairment as the causal mechanism. Stevens, Schiff, Lublin and Garber [1g] reported that elevation of blood urea associated with gastrointestinal bleeding was not due to impairment of renal function in the absence of shock. Christiansen [1a] attributed the azotemia to an intoxication from blood stagnating in the intestinal canal. Harkins and co-workers [1l, m] studied the problem by giving beef blood to dogs. They proposed a new term, "alimentary azotemia," and concluded that azotemia is due to absorption of digested blood and that starvation, dehydration, bleeding, hypochloremia and shock did not play a major part in its production. Yuile and Hawkins [1n] presented conclusions in essential agreement with those of Harkins. They emphasized the role of absorption of digested blood as the cause and stressed that comparable amounts of protein in the form of red blood cells, plasma, casein or lean meat cause similar increases.

At least two writers, Bookless [1s] and Alsted,[1c] have expressed the belief that the patients with the most pronounced azotemia are clinically uremic. Values of 190 and 216 mg. per hundred cubic centimeters of urea were obtained for 2

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Hoffman-LaRoche, Inc., supplied the heparin used in these studies.

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patients. While this viewpoint may be criticized on the basis that most modern opinions of the pathogenesis of uremia discredit any likelihood that retention of urea is responsible for the azotemia, the beliefs have been expressed and need answering at least to the extent of indicating whether treatment is needed for the elevated nitrogen level, and if so, what treatment. It is obvious that an understanding of the mechanism of the condition under discussion must be the basis for intelligent therapy.

Because of the disagreements referred to and the implications regarding therapy, this problem has been investigated again.

PLAN OF STUDY

All studies were made on dogs, 66 animals in all being employed. The study was made on experimental animals because we believe that it would be difficult, if not impossible, to evaluate the relative part played by several factors all of which might be present simultaneously in a given patient. Accordingly, we considered the various possibilities which might cause azotemia in a clinical case of bleeding from the upper part of the gastrointestinal tract. We have therefore experimentally evaluated each possibility separately and several combinations of possible causes. The causes considered and studied were (1) absorption of digested protein from the intestine, (2) effects of low blood pressure alone, (3) combinations of the preceding causes, (4) anemia, (5) dehydration as a result of deprivation of water and (6) renal damage due to absorption of some breakdown product of the blood in the intestine.

The dogs were fed well on Purina Dog Chow [2a] for several days and were then deprived of food for twelve to fifteen hours prior to the beginning of the observations. The experiments were controlled by estimating the values for blood urea nitrogen on 4 fasting dogs over twenty-eight hours and by giving 3 dogs respectively 14, 20 and 28.4 Gm. of homologous blood per kilogram of body weight by stomach tube and by giving 1 dog 13 Gm. of meat per kilogram. The blood urea nitrogen values were followed at various intervals up to twenty-two hours after the feeding, when they had returned to normal. The effect of blood in the gastrointestinal tract was studied by withdrawing blood rapidly from the external jugular vein, citrating it with 2.5 cc. of 10 per cent sodium citrate per hundred cubic centimeters of blood of one dog and giving it by stomach tube to another dog. When the combined effects of low blood pressure and absorption of digested protein were studied, blood was withdrawn from the jugular vein, citrated and given to the same dog by stomach tube. A uniform dose of 30 cc. of blood per kilogram was used in all experiments in which blood was fed. It is realized that this represents a large hemorrhage. The amount was deliberately made large with the belief that if results were not obtained with such amounts they would not be obtained with smaller amounts and with the knowledge that dogs withstand loss of large amounts of blood relatively safely. Lowered blood pressures were produced by puncture of the external jugular vein. The blood pressure was lowered to various levels, usually to 80 mm. of mercury or below. Thirty per cent of the calculated blood volume was removed initially. One to three additional bleedings were required to lower the blood pressure sufficiently in some animals. The blood volume was estimated as 8 per cent of the body weight. Blood pressures were determined by direct puncture of a femoral artery according to our modification of the method of Dameshek and Loman.[3] The effects of anemia were studied by following the blood urea nitrogen level in dogs made acutely anemic by bleeding and by giving blood from other dogs (30 cc. per kilogram) to dogs made severely anemic by previous bleeding. The effects of dehydration were noted by withholding water from twelve to twenty-four hours, during which time blood had been fed, the blood pressure lowered or these two procedures combined, and comparing the results obtained after the same procedures and after water had been given by stomach tube. Strangely, many of the dogs did not appear thirsty even after extreme hemorrhage—contrary to clinical experience with bleeding patients. The possible factor of the absorption from the intestine of a substance toxic to the kidney was studied by determining urea clearance before and during a period of digestion of blood. This was done during periods of normal and of low blood pressure. Urea clearance was also studied on some dogs with blood pressures lowered by bleeding. Studies of urea clearance were done by the method and standards of Summerville, Hanzal and Goldblatt [4] and determinations of urea were made by standard urease methods.[5]

Hematocrit studies and determinations of the specific gravity of both heparinized whole blood and heparinized plasma were performed routinely on all dogs to be sure our results were not complicated or confused by fluid shifts. The specific gravity of whole blood and of plasma was studied by the "falling drop" method of Barbour and Hamilton.[6]

2a. Following is the formula for Purina Dog Chow Checkers used in this experimental work:

	Per Cent
Protein	22.50
Fat	5.50
Fiber	3.75
Ash	7.00
Carbohydrates (nitrogen-free extract)	50.25
Moisture	11.00
Calcium	1.75
Phosphorus	1.00
Magnesium	0.11
Potassium	0.70
Soluble chlorides (as NaCl)	1.25
	Parts/Million
Iron	180.00
Copper	8.00
Cobalt	0.10
Manganese	75.00
Carotene	1.70

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RESULTS

I. Control studies.

Four fasting dogs were studied over a period of twenty-four to thirty hours to determine the effect on blood urea levels. The results are recorded in table 1. These results show some individual variations but in general show uniformity throughout the period of observation. They may be criticized on the ground that sampling was perhaps at too infrequent intervals.

TABLE 1.—*Control Blood Urea Nitrogen Values*

Dog No.	Weight, Kg.	Hematocrit, %	Blood Urea Nitrogen, Mg./100 Cc. Initially	After 4 Hr.	After 21 Hr.	After 26 Hr.	After 28 Hr.
9	12.0	41	16.1	23.8	22.0	24.5	23.4
10	10.0	40	12.6	18.2	16.8	16.5	14.0
11	12.6	44	15.4	17.5	13.3	16.1	13.8
12	13.4	44	16.1	14.7	14.7	13.6	13.3

In these experiments the animals were given 30 cc. of blood per kilogram in two equally divided doses, the second dose given two and one-half to three hours after the first. Care was observed to obtain dogs that were not unusually anemic, and estimations of hematocrit values and specific gravity of whole blood and of plasma were made.

From these data it can be seen that the urea nitrogen level of the blood invariably rises after the giving of blood by stomach tube. The elevation is apparent within an hour after the blood has been given; the level is well elevated within two to three hours, has reached a peak in about six hours and has returned to within approximately normal range within twelve hours.

While the time relationships of the blood urea nitrogen elevation are uniform, the extent of the elevation is decidedly lacking in uniformity despite the fact that a uniform dose of blood was given to all dogs. This dose was large, 30 cc. of blood per kilogram. But in spite of this the elevation of blood urea nitrogen is not always great (dogs 60 and 62).

TABLE 2.—*Effect of Variable Amounts of Blood and Meat on Blood Urea Nitrogen Levels*

Dog No.	Weight, Kg.	Blood per Kg., Cc.	Meat per Kg., Gm.	Blood Urea Nitrogen Mg. per 100 Cc. Fasting	After Giving of Blood or Meat *							
					(0:30)	(1:35)	(3:0)	(4:38)	(10:50)	(18:0)	(22:25)	(26:45)
2	17.2	14.0	..	9.5	10.3	13.7	18.9	23.8	14.7	10.9	10.9	8.1
					(0:40)	(2:15)	(4:20)	(6:30)	(8:12)	(11:57)	(21:55)	
4	9.5	28.4	..	12.6	14.7	27.2	35.7	39.3	30.8	21.3	14.9	
					(1:17)	(2:55)	(4:30)	(6:20)	(8:55)	(13:10)	(22:25)	
5	12.5	20.0	..	12.7	15.1	28.7	37.0	33.5	28.11	19.6	12.0	
					(0:45)	(2:20)	(4:14)	(6:18)	(8:11)	(11:55)	(21:55)	
2	17.0	....	13	13.9	11.6	14.0	15.4	16.4	14.4	12.3	12.0	

* The figures in parentheses indicate the time (hours:minutes) after blood or meat was given.

Control experiments were also done to show the relation of the effects of various amounts of blood and the similar effects obtained by feeding meat. Table 2 contains the data obtained. These data show that the rise begins within thirty minutes after the blood is given, reaches its peak from four and one-half to six hours after ingestion of blood and returns to within normal range in approximately twelve hours, although approximately eighteen hours is required for its return to fasting levels.

Table 2 also shows that the elevation of blood urea nitrogen following ingestion of meat is of the same character as that obtained from ingestion of blood. The rise following ingestion of meat, lesser by comparison, is due to the fact that 13 Gm. of meat per kilogram contains considerably less protein than 14 cc. of blood per kilogram.

II. Effect of feeding blood on the blood urea nitrogen level.

Table 3 contains the data obtained from a study of 6 dogs fed blood and not allowed water for the first twenty-four hours of the experiment.

The results of hematocrit studies and determinations of specific gravity on blood and plasma indicate that the increase in the blood urea values are probably not due to fluid shifts such as might concentrate the blood components. These values show the reverse, if anything. In all 6 dogs of this group there was a consistent fall in the hematocrit values and specific gravity of whole blood and plasma. The significance of this apparent dilution of the blood is difficult to understand in view of the restriction of water during the first twenty-four hours. Conceivably it could be due to absorption of the water in the blood itself and the water resulting from the metabolism of the digested protein. The decrease in the specific gravity of the plasma may also be contributed to by the fact that blood plasma proteins are being consumed for metabolic needs.

TABLE 3.—*Effects of Ingested Blood on Urea Nitrogen Levels*

No Water for First Twenty-Four Hours

	Interval After First Bleeding		Blood Fed, Cc.*	Blood Urea Nitrogen, Mg./100 Cc.	Hematocrit, per Cent	Specific Gravity		Blood Pressure, Mm. Hg	Urea Clearance, Cc./Min.
	Hr.	Min.				Blood	Plasma		
Dog 17									
Weight, 13 Kg.									
	Control		195	8.7	32.4	1.0470	1.0223	...	....
	3	28	195	18.9	35.2	1.0490	Lost		
	6	28	...	23.5	34.7	1.0473	1.0232	...	....
	9	7	...	21.2	32.2	1.0466	1.0227	...	....
	12	..	...	15.5	30.5	1.0442	1.0227	...	....
	19	47	...	12.9	34.9	1.0481	1.0220	...	....
	24	10	...	11.5	30.0	1.0458	1.0227	...	....
	28	22	...	12.5	31.0	1.0452	1.0231	...	....
	35	45	...	10.5	31.7	1.0464	1.0228	...	....
	45	85	...	9.8	32.2	1.0459	1.0231	...	....
Dog 18									
Weight, 15 Kg.									
	Control		210	11.8	35.2	1.0539	1.0279	...	....
	3	17	207	23.8	34.8	1.0535	1.0284	...	....
	6	17	...	32.2	30.7	1.0503	1.0281	...	....
	8	57	...	26.0	33.2	10.573	1.0276	...	....
	11	48	...	19.7	29.7	1.0495	1.0276	...	....
	19	39	...	14.4	32.5	1.0508	1.0276	...	....
	23	59	...	14.0	29.9	1.0495	1.0268	...	....
	28	18	...	12.6	32.7	1.0514	1.0273	...	....
	35	37	...	14.0	32.7	1.0517	1.0271	...	....
	45	49	...	12.6	33.5	1.0515	1.0272	...	....
Dog 22									
Weight, 11.4 Kg.									
	Control		171	13.3	50.0	1.0612	1.0254	...	....
	2	3	171	35.7	49.8	1.0612	1.0262	...	....
	4	22	...	41.5	47.2	1.0592	1.0262	...	....
	7	..	...	50.0	43.4	1.0564	1.0253	...	....
	9	49	...	40.0	47.0	1.0572	1.0256	...	....
	12	44	...	26.6	44.5	1.0574	1.0250	...	....
	23	58	...	19.0	44.8	1.0578	1.0252	...	....
	30	54	...	12.6	44.4	1.0548	1.0235	...	....
	36	46	...	11.9	38.0	1.0506	1.0226	...	....
	47	18	...	13.3	45.0	1.0554	1.0237	...	....
Dog 58									
Weight, 7.7 Kg.									
	Control		116	13.3	46.4	1.0553	1.0233	124	36.8
	2	..	116	17.3	38.9	1.0505	1.0225	132	....
	4	27	...	23.1	39.0	1.0507	1.0226	...	....
	5	19	...	22.8	43.8	1.0536	1.0229	...	....
	6	23	...	20.7	39.0	1.0500	1.0222	...	....
	7	22	...	15.4	38.0	1.0497	1.0227	...	38.1
	9	42	...	10.5	37.0	1.0491	1.0226	...	....
	12	49	...	6.9	39.3	1.0511	1.0220	126	....
	22	31	...	6.7	43.0	1.0538	1.0233	...	....
	28	50	...	7.7	34.0	1.0466	1.0219	...	....
	47	1	...	7.5	41.0	1.0577	1.0231	116	....
	48	..	...	6.7	39.0	1.0500	1.0226	...	42.8
	49	4	...	5.9	39.5	1.0509	1.0224	...	....
Dog 60									
Weight, 7.9 Kg.									
	Control		119	3.5	34.0	1.0478	1.0229	104	75.8
	1	51	119	8.5	32.8	1.0473	1.0225	...	....
	4	1	...	15.2	34.5	1.0475	1.0234	...	....
	4	55	...	11.6	33.5	1.0477	1.0228	...	....
	5	55	...	12.8	31.0	1.0442	1.0216	...	....
	7	3	...	11.9	30.0	1.0436	1.0213	...	49.7
	9	22	...	3.5	29.3	1.0432	1.0212	...	....
	11	53	...	2.1	28.0	1.0431	1.0211	106	....
	22	16	...	2.1	32.0	1.0441	1.0209	107	....
	26	14	...	3.2	29.8	1.0432	1.0200	103	....
	27	18	...	2.8	28.4	1.0426	1.0196	...	....
	28	24	...	2.9	27.8	1.0427	1.0196	...	84.2
Dog 62									
Weight, 4.6 Kg.									
	Control		69	5.7	33.9	1.0559	1.0236	...	67.2
	..	55	..	8.4	31.2	1.0479	1.0231	129	....
	2	12	69	12.2	32.5	1.0479	1.0227	130	....
	4	37	...	11.8	31.2	1.0427	1.0221	...	....
	5	15	...	12.7	28.5	1.0389	1.0216	134	....
	6	14	...	11.0	29.4	1.0434	1.0217	...	....
	7	11	...	10.1	28.0	1.0422	1.0215	...	....
	8	48	...	8.3	28.0	1.0424	1.0217	...	51.7
	12	17	...	5.6	28.0	1.0428	1.0213	138	....
	22	44	...	3.8	26.0	1.0420	1.0220	124	....
	27	25	...	5.6	28.0	1.0430	1.0220	132	....
	28	22	...	6.8	27.7	1.0428	1.0215	...	....
	29	31	...	5.9	27.2	1.0426	1.0216	...	48.8
	48	45	...	6.3	26.3	1.0422	1.0218	119	....
	49	45	...	6.0	25.2	1.0416	1.0218	...	....

* Total dose of blood (30 cc. per kilogram of body weight) fed by stomach tube in two doses of 15 cc. per kilogram.

TABLE 4.—*Effects of Lowered Blood Pressure by Bleeding on Blood Urea Nitrogen Levels*

No Water Given During First Twelve to Twenty-Four Hours

	Interval After First Bleeding		Bled, Cc.	Blood Urea Nitrogen, Mg./100 Cc.	Hematocrit, per Cent	Specific Gravity		Blood Pressure, Mm. Hg	Urea Clearance, Cc./Min.
	Hr.	Min.				Blood	Plasma		
Dog 15 Weight, 9.8 Kg.									
	Control		215	12.6	48.3	1.0609	1.0292	120	....
	2	35	105	**16.1**	45.5	1.0571	1.0284	110	....
	4	36	85	18.3	45.0	1.0546	1.0273	100	....
	8	..	...	25.6	43.0	1.0526	1.0271	60	....
	10	50	(52%)*	31.0	41.3	1.0523	1.0272	60	....
	13	42	...	33.0	40.0	1.0516	**1.0274**	70	....
	22	4	...	26.8	32.7	1.0455	1.0263	92	....
	25	58	...	24.0	31.0	1.0472	1.0256	102	....
	30	40	...	19.6	28.7	1.0449	1.0256	...	....
	37	30	...	14.3	21.9	1.0443	1.0251	...	....
	47	50	...	11.2	25.5	1.0428	1.0259	102	....
Dog 16 Weight, 13.9 Kg.									
	Control		285	13.9	42.0	1.0556	1.0254	140	....
	2	10	150	13.3	31.8	1.0450	1.0226	126	....
	4	16	140	**16.1**	25.2	1.0391	1.0220	110	....
	7	30	90	15.4	33.1	1.0445	1.0232	100	....
	10	15	65	16.1	30.3	1.0432	1.0229	106	....
	13	15	...	16.1	29.7	1.0425	1.0226	86	....
	21	13	(65.5%)*	16.8	24.2	1.0384	1.0233	90	....
	25	27	...	13.9	25.2	1.0426	1.0239	120	....
	29	49	...	13.9	22.3	1.0390	1.0236	...	....
	37	..	...	11.2	25.8	1.0422	1.0241	...	....
	47	14	...	9.1	26.0	1.0428	1.0249	120	....
Dog 17 Weight, 14 Kg.									
	Control		255	13.3	50.1	1.0614	1.0239	160	....
	2	3	200	14.0	45.5	1.0568	1.0227	152	....
	4	13	100	15.4	39.3	1.0504	1.0212	130	....
	6	48	100	15.8	36.8	1.0490	1.0209	110	....
	9	38	95	17.8	35.6	1.0484	1.0212	92	....
	13	45	...	20.0	36.4	1.0489	1.0213	78	....
	23	59	(65%)*	15.8	29.5	1.0450	1.0216	97	....
	31	..	...	14.0	26.2	1.0401	1.0206	...	....
	36	47	...	14.7	22.0	1.0381	1.0204	90	....
	47	15	...	8.8	19.8	1.0372	1.0212	96	....
Dog 18 Weight, 12.3 Kg.									
	Control		260	12.6	44.0	1.0582	1.0266	160	....
	2	1	195	15.1	40.2	1.0535	1.0248	160	....
	3	58	200	17.5	37.1	1.0507	1.0242	130	....
	6	35	90	21.0	37.0	1.0507	1.0244	96	....
	9	14	...	28.8	33.0	1.0484	1.0241	76	....
	13	17	(70%)*	38.5	32.5	1.0488	1.0246	72	....
	23	33	...	**38.5**	27.7	1.0458	1.0250	110	....
	30	98	...	25.8	24.0	1.0405	1.0229	...	....
	36	21	...	19.6	23.0	1.0406	1.0233	105	....
	46	58	...	6.4	19.3	1.0385	1.0229	146	....
Dog 19 Weight, 9.7 Kg.									
	Control		225	14.6	53.0	1.0628	1.0266	166	57.9
	..	56	160	13.7	52.8	1.0612	1.0252	148	....
	2	20	...	16.8	49.5	1.0565	1.0240	67	....
	3	26	70	19.8	47.5	1.0558	1.0242	78	....
	4	56	...	21.0	44.0	1.0541	1.0240	50	....
	7	10	(58.6%)*	27.8	43.0	1.0550	1.0240	50	....
	8	42	...	**28.9**	42.5	1.0545	1.0245	...	....
	9	53	...	33.1	42.0	1.0538	1.0242	51	0
	12	26	...	38.4	38.0	1.0502	1.0230	58	....
	22	20	...	37.1	32.1	1.0481	1.0239	80	....
	27	35	...	**28.0**	30.0	1.0459	1.0237	92	....
	28	43	...	34.0	28.0	1.0436	1.0225	92	25.8
	35	13	...	26.8	25.0	1.0424	1.0231	94	....
	46	42	...	17.5	23.0	1.0421	1.0238	108	....
	47	47	...	17.5	21.3	1.0408	1.0231	...	25.1
Dog 55 Weight, 11 Kg.									
	Control		245	5.6	44.4	1.0567	1.0261	146	57.3
	1	2	190	7.7	37.0	1.0505	1.0238	118	....
	2	3	45	13.3	34.7	1.0470	1.0228	67	....
	3	34	..	17.5	34.0	1.0470	1.0233	62	....
	5	40	50	**21.2**	33.5	1.0472	1.0238	72	....
	7	22	..	18.2	30.0	1.0450	1.0231	56	....
	9	2	(60%)*	**28.0**	30.0	1.0441	1.0233	53	....
	10	..	...	27.3	28.2	1.0434	1.0230	57	0
	12	46	...	26.3	27.0	1.0427	1.0233	64	....
	23	23	...	24.2	23.2	1.0389	1.0234	95	....
	28	56	...	12.6	19.9	1.0381	1.0237	95	....
	30	13	...	7.6	20.2	1.0369	1.0235	...	24.5
	52	9	...	**7.0**	18.8	1.0372	1.0244	112	....
	53	9	...	4.2	18.5	1.0372	1.0244	...	29.7
Dog 57 Weight, 9 Kg.									
	Control		216	10.5	37.2	1.0488	1.0227	121	41.1
	..	56	100	11.5	30.0	1.0425	1.0204	108	....
	2	4	40	10.8	27.7	1.0399	1.0199	67	....
	3	42	50	13.7	26.0	1.0384	1.0199	70	....
	5	22	..	20.9	23.0	1.0351	1.0194	62	....
	7	24	30	20.4	21.5	1.0336	1.0189	66	....
	8	49	..	19.1	19.5	1.0319	1.0186	58	2.3
	9	49	(60.5%)*	19.9	18.2	1.0313	1.0186	61	....
	12	58	...	**26.1**	15.8	1.0308	1.0186	60	....
	22	50	...	30.9	13.9	1.0296	1.0195	64	....
	27	50	...	**19.8**	13.0	1.0292	1.0198	64	....
	28	53	...	20.8	13.0	1.0287	1.0197	..	16.1
	46	52	...	10.1	12.0	1.0286	1.0206	96	....
	47	58	...	9.2	11.5	1.0287	1.0206	..	....
	49	5	...	9.6	11.4	1.0287	1.0206	..	27.4

* Total per cent of calculated blood volume removed.

TABLE 5.—*Effects of a Combination of Feeding Blood and Low Blood Pressure (Produced by Bleeding) on Blood Urea Nitrogen Levels*

	Interval After First Bleeding		Bled, Cc.	Fed Blood, Cc.	Blood Urea Nitrogen, Mg./100 Cc.	Hematocrit, per Cent	Specific Gravity		Blood Pressure, Mm. Hg	Urea Clearance, Cc./Min.
	Hr.	Min.					Blood	Plasma		
Dog 27										
Weight, 8.4 Kg.										
	Control		225	126	15.4	46.3	1.0577	1.0260	140	....
	1	57	150	126	23.8	37.0	1.0492	1.0224	128	....
	4	5	100	...	31.5	26.3	1.0418	1.0203	117	....
	6	30	...	...	35.7	25.4	1.0397	1.0204	65	....
	9	30	45	...	34.3	25.4	1.0394	1.0218	80	....
	13	41	...	...	34.3	22.8	1.0375	1.0210	72	....
	23	33	...	...	27.3	19.9	1.0356	1.0216	92	....
	31	10	...	...	19.7	16.0	Clot	1.0216	101	....
	37	18	...	...	17.0	16.0	1.0331	1.0219	114	....
	47	35	...	...	13.4	15.5	1.0321	1.0226	104	....
Dog 28										
Weight, 11.5 Kg.										
	Control		225	173	11.9	47.1	1.0582	1.0261	137	....
	2	..	150	173	12.6	40.0	1.0526	1.0241	132	....
	3	50	125	...	11.2	36.4	1.0484	1.0226	107	....
	6	4	120	...	12.6	31.8	1.0451	1.0216	96	....
	9	20	60	...	15.4	28.8	1.0423	1.0216	78	....
Animal found dead next morning										
Dog 29										
Weight, 9.8 Kg.										
	Control		230	147	27.3	34.0	1.0476	1.0243	130	....
	2	5	150	147	27.3	27.0	1.0407	1.0221	114	....
	4	25	100	...	30.8	22.5	1.0367	1.0207	85	....
	6	41	60	...	30.9	22.4	1.0363	1.0213	80	....
	9	45	60	...	37.3	21.5	1.0338	1.0215	80	....
	13	9	...	...	55.0	17.0	1.0311	1.0209	45	....
Dog died during night										
Dog 30										
Weight, 9.5 Kg.										
	Control		225	143	14.0	32.9	1.0490	1.0248	140	....
	2	10	150	143	22.4	30.0	1.0450	1.0225	98	....
	4	25	100	...	28.8	22.6	1.0285	1.0212	86	....
	6	45	55	...	41.0	22.2	1.0275	1.0215	70	....
	9	45	50	...	48.0	22.3	1.0279	1.0220	75	....
	12	35	...	...	52.0	20.0	1.0255	1.0220	65	....
	22	40	...	...	44.0	17.5	1.0251	1.0224	72	....
	29	40	...	...	29.0	15.3	1.0230	1.0223	80	....
	36	25	...	...	14.0	14.8	1.0216	1.0220	90	....
	47	45	...	...	9.0	13.8	1.0216	1.0224	88	....
	54	35	...	...	9.3	13.0	1.0209	1.0224	92	....
Dog 31										
Weight, 9.5 Kg.										
	Control		254	131	13.4	51.2	1.0610	1.0266	152	....
	1	50	125	131	24.6	32.4	1.0468	1.0218	112	....
	4	3	70	...	50.0	32.7	1.0450	1.0207	96	....
	5	58	50	...	69.0	28.7	1.0406	1.0201	90	....
	9	10	40	...	80.0	25.3	1.0394	1.0206	76	....
	12	52	30	...	73.5	23.2	1.0384	1.0209	76	....
	22	5	...	...	36.3	22.5	1.0376	1.0225	80	....
	29	46	...	...	20.2	20.5	1.0359	1.0229	100	....
	36	8	...	...	13.4	17.9	1.0338	1.0222	92	....
	46	40	...	...	11.9	21.0	1.0368	1.0240	96	....
Dog 32										
Weight, 7.8 Kg.										
	Control		220	117	8.7	34.7	1.0498	1.0265	120	....
	1	45	100	127	15.0	28.2	1.0433	1.0233	100	....
	3	48	55	...	24.6	26.7	1.0413	1.0221	85	....
	5	40	..	...	36.5	23.6	1.0386	1.0223	70	....
	8	55	60	...	37.0	20.6	1.0364	1.0215	92	....
	12	33	...	...	43.0	18.5	1.0330	1.0217	78	....
	21	50	...	...	38.5	18.4	1.0335	1.0233	92	....
	29	25	...	...	33.0	16.5	1.0323	1.0229	94	....
	35	50	...	...	13.4	13.6	1.0301	1.0216	93	....
	46	24	...	...	14.0	15.0	1.0324	1.0230	98	....
Dog 52										
Weight, 10.2 Kg.										
	Control		245	158	11.5	27.0	1.0450	1.0286	105	52.1
	1	34	150	...	19.7	21.8	1.0392	1.0252	82	....
	2	42	...	158	29.3	18.0	1.0335	1.0232	56	....
	4	47	50	...	35.0	17.5	1.0325	1.0231	78	....
	6	40	...	...	28.8	15.0	1.0311	1.0223	58	....
	8	12	...	...	45.2	15.0	1.0313	1.0225	46	10.1
	9	9	...	...	42.9	14.8	1.0311	1.0224	60	....
	12	9	...	...	37.0	13.7	1.0310	1.0226	55	....
	22	25	...	...	51.7	12.5	1.0307	1.0230	56	....
	28	12	...	...	56.0	12.0	1.0296	1.0227	60	....
	34	22	...	...	46.8	10.5	1.0299	1.0231	63	....
	45	59	...	...	47.6	10.8	1.0310	1.0241	67	....
	47	9	...	...	46.5	11.0	1.0304	1.0238	..	7.0
	48	9	...	...	47.2	10.8	1.0306	1.0240	76	....
	52	37	...	...	38.5	10.5	1.0303	1.0242	79	....
	58	44	...	...	22.5	10.5	1.0307	1.0233	90	....
	68	29	...	...	18.2	10.0	1.0304	1.0241	92	15.7
	69	32	...	...	16.1	10.0	1.0303	1.0242	..	....
	70	29	...	...	16.2	10.0	1.0300	1.0242	..	....
	125	37	...	...	17.1	10.2	1.0322	1.0259	98	....
	126	40	...	...	17.5	10.2	1.0318	1.0258	..	24.4
	148	11	...	...	20.3	10.5	1.0313	1.0259	110	....
	149	38	...	...	21.0	10.5	1.0316	1.0259	...	20.0

TABLE 5.—*Effects of a Combination of Feeding Blood and Low Blood Pressure (Produced by Bleeding) on Blood Urea Nitrogen Levels—Continued*

	Interval After First Bleeding		Bled, Cc.	Fed Blood, Cc.	Blood Urea Nitrogen, Mg./100 Cc.	Hematocrit, per Cent	Specific Gravity		Blood Pressure, Mm. Hg	Urea Clearance, Cc./Min.
	Hr.	Min.					Blood	Plasma		
Dog 54 Weight, 7.8 Kg.										
	Control		190	117	7.0	36.4	1.0502	1.0260	136	49.5
	..	47	117	...	8.5	30.0	1.0439	1.0228	120	....
	2	15	...	117	12.3	24.5	1.0384	1.0221	63	....
	3	16	75	...	13.3	24.0	1.0388	1.0221	72	....
	4	57	...	...	17.3	20.5	1.0336	1.0201	65	....
	6	59	40	...	19.3	18.4	1.0324	1.0200	75	....
	8	30	...	...	28.0	16.0	1.0301	1.0194	58	3.2
	9	40	...	...	22.8	16.0	1.0307	1.0199	56	....
	12	7	...	...	27.9	15.3	1.0319	1.0203	54	....
Dog 56 Weight, 8.0 Kg.										
	Control		190	120	6.6	39.4	1.0519	1.0237	138	36.1
	1	..	120	...	9.7	35.0	1.0486	1.0219	100	....
	1	50	50	120	13.0	34.8	1.0467	1.0215	80	....
	3	8	40	...	18.9	33.0	1.0447	1.0210	78	....
	5	21	40	...	26.4	28.5	1.0428	1.0208	72	....
	6	59	40	...	25.2	24.8	1.0377	1.0196	70	....
	8	39	...	...	30.8	23.5	1.0355	1.0199	67	17.4
	9	43	...	...	32.2	22.2	1.0354	1.0196	64	....
	12	18	...	...	31.2	20.1	1.0329	1.0196	69	....
	22	57	...	...	11.2	17.0	1.0324	1.0204	90	....
	28	36	...	...	8.1	16.8	1.0324	1.0208	100	....
	29	47	...	...	4.9	15.6	1.0312	1.0204	...	49.4
	51	50	...	...	3.4	15.2	1.0323	1.0215	112	....
	52	46	...	...	3.4	14.6	1.0321	1.0217	...	57.5
Dog 59 Weight, 10 Kg.										
	Control		240	150	10.5	52.0	1.0614	1.0254	165	36.8
	1	20	60	150	12.2	42.3	1.0534	1.0227	116	....
	2	49	100	...	14.6	42.5	1.0519	1.0222	82	....
	4	47	100	...	24.4	37.5	1.0479	1.0211	79	....
	7	30	...	...	30.8	30.0	1.0445	1.0205	27	....
	8	53	...	...	38.2	33.0	1.0456	1.0212	17	....
	9	5	Died							
Dog 61 Weight, 5.8 Kg.										
	Control		140	87	11.3	45.3	1.0559	1.0242	117	41.1
	1	4	98	...	14.0	35.0	1.0479	1.0206	121	....
	2	22	75	87	19.6	36.5	1.0479	1.0202	84	....
	3	53	...	...	26.9	30.0	1.0427	1.0187	52	....
	4	53	25	...	31.7	26.7	1.0389	1.0177	68	....
	6	36	...	...	39.4	23.7	1.0352	1.0172	55	....
	7	47	...	...	47.5	22.8	1.0384	1.0177	54	....
	9	3	...	...	54.6	21.8	1.0348	1.0178	56	6.2
	10	11	...	...	51.7	22.0	1.0346	1.0182	55	....
	12	17	...	...	51.3	21.0	1.0345	1.0186	53	....
	22	37	...	...	20.3	18.0	1.0333	1.0195	81	....
	27	20	...	...	11.8	17.5	1.0321	1.0198	78	....
	28	22	...	...	11.2	16.5	1.0321	1.0194	...	31.3
	29	32	...	...	10.0	15.8	1.0315	1.0195	75	....
	47	39	...	...	11.8	14.0	1.0316	1.0215	84	....
	48	42	...	...	11.8	13.2	1.0316	1.0214	...	26.5

Determinations of blood pressure were made on dogs 58, 60 and 62. It will be noted that the pressures remained normal throughout the experiment. The elevation of blood urea nitrogen was in no way therefore due to lowering of the blood pressure by the absorption from the intestine of a vasodilating substance produced by the digestion of blood.

Studies of urea clearance were also made on dogs 58, 60 and 62. The values were at all times normal and therefore indicate that the elevation of blood urea nitrogen due to blood in the intestine is not caused by the absorption from the intestine of a nephrotoxic substance which decreases renal function.

III. Effect on the blood urea nitrogen of a lowered blood pressure due to bleeding.

Table 4 contains the data obtained from the study of 7 dogs, on 3 of which studies of urea clearance were made. Water was withheld for the first twelve to twenty-four hours of the experiment. The data show that there may be an extensive elevation of the urea nitrogen levels following bleeding. The following conclusions seem justified: While there is a very slight rise in the urea nitrogen values regardless of the effects on the blood pressure, the rise in urea nitrogen is not beyond the normal range unless the systolic blood pressure is lowered to less than 80 mm. The slight rise in blood urea

nitrogen in most of the dogs in this group before the systolic pressure was reduced to below 80 mm. may have been due to the handling of the dogs and is probably an insignificant normal variation, but most probably it was due to the fact that blood pressures were taken and if found not down to significantly low levels the animal was bled. The pressures were not taken at the end of the bleeding but at approximately two hour intervals after the previous bleeding. It seems likely that the pressure was down for a period after each bleeding but may have come back before the next reading of pressure was taken.

When the pressures are reduced to 80 mm. or below and maintained there, a characteristic curve results. The blood urea nitrogen goes up slowly, reaches a peak in twelve to twenty-four hours and slowly falls. This is in contradistinction to the quicker rise and fall seen when blood is given by stomach tube.

Studies on dogs 53, 55 and 57 show that there is a great reduction in renal function coincidental with the peak elevation of blood urea nitrogen and with the greatest reduction in blood pressure. With return of the blood pressure to normal levels, the urea clearance increases toward or to normal values.

The hematocrit values and specific gravity of blood and plasma in this group of dogs show progressively the changes characteristic of those which follow hemorrhage. No type of fluid shift which would confuse the interpretations is manifested by these results.

It is concluded from the study of the data obtained from this group of dogs that the loss of blood alone may result in elevation of the blood urea nitrogen if the loss of blood sufficiently lowers the blood pressure. In this group of dogs the critical level of pressure appears to be about 80 mm. of mercury systolic.

We interpret the data to indicate that the elevation of urea nitrogen associated with the external loss of blood is due to diminished renal function which results from lowering the blood pressure.

IV. Effect on the blood urea nitrogen of a combination of lowering the blood pressure by bleeding and feeding of blood.

Eleven dogs were studied in this group. On 5 of the 11 studies of urea clearance were made. In general, the combination of procedures (bleeding and feeding blood) results in the early rise of urea nitrogen characteristic of feeding blood, the prolonged rise characteristic of lowered pressure and a greater rise than is characteristic of either procedure alone. In general, also, it is seen that the systolic blood pressure must be reduced below the critical level of about 80 mm of mercury to produce decided and prolonged rises in blood urea nitrogen. It may also be noted that the peak values for the blood urea nitrogen coincided usually with the greatest fall in blood pressure, and the lowest values for urea clearance coincided with both.

TABLE 6.—*Effect of Severe Anemia on Urea Nitrogen After Feeding of 30 Cc./Kg. of Whole Blood*

	Interval After First Bleeding		Blood Fed, Cc.	Blood Urea Nitrogen, Mg. per 100 Cc.	Hematocrit, %	Specific Gravity	
	Hr.	Min.				Blood	Plasma
Dog 23							
Weight, 9.8 Kg.							
Control			147	17.5	28.3	1.0419	1.0267
	2	28	147	24.5	22.8	1.0432	1.0293
	4	6	...	30.8	23.7	1.0424	1.0268
	6	2	...	34.5	24.8	1.0424	1.0267
	9	12	...	35.0	23.9	1.0413	1.0267
	12	33	...	27.3	22.8	1.0419	1.0273
	21	46	...	21.0	25.2	1.0445	1.0277
	25	18	...	19.0	23.0	1.0421	1.0271
	32	58	...	17.5	23.1	1.0417	1.0268
	48	19	...	17.5	24.0	1.0424	1.0269
Dog 24							
Weight, 13.5 Kg.							
Control			202	8.4	21.8	1.0392	1.0242
	2	25	202	16.8	24.3	1.0409	1.0248
	4	..	...	26.5	22.8	1.0402	1.0250
	5	55	...	30.8	22.5	1.0397	1.0256
	9	5	...	21.0	21.3	1.0389	1.0253
	12	26	...	17.5	20.8	1.0387	1.0248
	21	40	...	14.0	22.0	1.0401	1.0249
	25	11	...	15.3	24.4	1.0384	1.0249
	35	52	...	8.4	23.8	1.0398	1.0249
	48	12	...	5.6	24.0	1.0409	1.0249
Dog 25							
Weight, 13.4 Kg.							
Control			201	18.2	26.5	1.0421	1.0229
	2	22	201	22.5	22.8	1.0389	1.0218
	3	54	...	28.0	22.6	1.0379	1.0215
	5	51	...	33.0	25.9	1.0419	1.0233
	9	..	...	23.0	26.2	1.0421	1.0233
	12	20	...	18.2	25.3	1.0410	1.0223
	21	34	...	14.0	26.8	1.0427	1.0228
	25	5	...	14.0	22.9	1.0394	1.0223
	32	46	...	10.5	21.8	1.0373	1.0215
	48	7	...	8.4	22.1	1.0386	1.0221
Dog 26							
Weight, 12.4 Kg.							
Control			186	25.0	25.5	1.0429	1.0249
	2	22	186	28.7	25.9	1.0441	1.0256
	3	50	...	37.0	26.9	1.0448	1.0259
	5	47	...	45.0	24.5	1.0417	1.0248
	8	54	...	30.0	22.0	1.0392	1.0238
	12	13	...	22.4	22.3	1.0400	1.0238
	21	29	...	21.0	23.6	1.0411	1.0240
	24	59	...	21.8	19.7	1.0376	1.0231
	32	40	...	14.6	21.7	1.0381	1.0233
	48	1	...	10.5	20.6	1.0376	1.0225

V. Effect on the blood urea nitrogen of anemia due to bleeding.

It may be ascertained from a study of the data in tables 4 and 5 that anemia itself, even of severe grades, is not sufficient to cause elevation of the blood urea nitrogen. For example, dog 57 (table 4) had a blood urea nitrogen level of

9.6 mg. per hundred cubic centimeters with a hematocrit value of 11.4 per cent. Similarly dog 30 (table 5) had a value for blood urea nitrogen of 9.3 mg. per hundred cubic centimeters and a hematocrit value of 13 per cent. Many other dogs mentioned in tables 4 and 5 showed similar relationships, but these 2 exemplify the point better. Dog 63 (table 7) also

TABLE 7.—*Effect of Severe Anemia on Renal Function as Measured by Urea Clearance*

Interval After First Bleeding, Days	Bled, Cc.*	Blood Urea Nitrogen, Mg. per 100 Cc.	Hematocrit, %	Specific Gravity: Blood	Specific Gravity: Plasma	Blood Pressure, Mg. Hg	Urea Clearance, Cc. per Min.
Dog 63 Weight, 5.8 Kg.							
Control	338	11.3	45.3	1.0559	1.0242	117	41.1
2	...	11.8	13.2	1.0316	1.0214	84	26.5
7	...	8.2	16.2	1.0333	1.0224	91	32.0
Dog 64 Weight, 7.2 Kg.							
Control	365	14.5	42.5	1.0577	1.0292	146	38.9
	150	....	19.1	1.0377	1.0255	112	....
	50	....	13.7	1.0322	1.0231	106	....
7	...	9.3	15.6	1.0353	1.0263	120	29.7
Dog 67 Weight, 7.7 Kg.							
Control	...	13.3	46.4	1.0553	1.0233	132	36.8
2	250	6.4	38.4	1.0497	1.0227	116	42.8
20	350	14.6	28.0	1.0434	1.0237	...	35.7
23	110	....	15.4	1.0317	1.0228	100	....
24	40	....	13.4	1.0308	1.0229	90	....
27	242	19.7	13.0	1.0330	1.0254	100	27.1
	(261 cc. of plasma returned)						
31	...	....	9.0	1.0311	1.0254	89	18.7
Dog 65 Weight, 9.0 Kg.							
Control	436	10.5	37.2	1.0488	1.0227	121	41.1
2	...	10.1	12.0	1.0286	1.0206	96	27.4
20	...	12.5	12.5	1.0300	1.0238	105	16.4
23	...	....	12.4	1.0303	1.0261	110	....
24	...	....	13.8	1.0321	1.0258	100	....
27	...	29.9	15.0	1.0338	1.0279	96	25.8
28	Died						
Dog 67 Weight, 4.6 Kg.							
Control	...	5.7	33.9	1.0559	1.0236	129	67.2
2	...	6.8	26.8	1.0422	1.0218	119	79.2
7	...	8.2	30.3	1.0439	1.0215	138	37.8
8	250						
10	220	....	18.4	1.0333	1.0210	120	....
11	158	....	13.6	1.0300	1.0206	128	....
14	...	12.6	13.2	1.0318	1.0240	110	24.6
	Died						

* Bled by puncture of the jugular vein after determinations were made.

clearly showed that even severe anemia does not suffice to cause an elevation of blood urea nitrogen.

VI. Effect on the blood urea nitrogen of giving anemic dogs 30 cc. per kilogram of whole blood and of anemia on renal function as measured by urea clearances.

Table 6 contains the data pertaining to our study of the combined effects of feeding blood and anemia on the blood urea nitrogen. Four dogs made anemic by previous bleeding, usually a number of days before, served as the subjects of this phase of the experiment.

Comparison of the data in table 6 and table 3 shows that there is no greater rise in the blood urea nitrogen produced by giving 30 cc. of blood per kilogram to anemic dogs than results from giving blood to dogs with normal hematocrit values. Hematocrit levels of about 50 per cent of the normal were present in several instances.

Table 7 contains the data for 5 dogs on which the effect of anemia on the urea clearances were studied. Urea clearances were determined on dogs with normal or slightly low hematocrit levels. By bleeding these animals, the hematocrit values were gradually reduced, in some instances to rather low levels, and the urea clearance was determined at intervals as the hematocrit levels were reduced by repeated bleedings.

Analysis of the data presented in tables 6 and 7 does not result in an entirely clear concept concerning the effect of anemia on urea clearance. The data, however, appear to warrant the following conclusions: Moderate decrease in the hematocrit values is not associated with a decrease in urea clearance. While severe anemia is associated with a decrease in the urea clearance as compared with the control level obtained when hematocrit values are normal, this decreased level may still be well within the range of normal for dogs in general. In some instances (dog 65) the striking decrease was also associated with a low blood pressure. While there appears to be a definite decrease in urea clearance as a result of a severe anemia, this anemia alone is never the cause of an elevated blood urea nitrogen level.

VII. Effect of forcing of water on the urea nitrogen level following ingestion of 30 cc. of blood per kilogram in two equal doses.

Comparison of the results in table 8 with those recorded in table 3 will show that the giving of 10 cc. of water per kilogram by tube to 2 dogs and as much as 50 cc. per kilogram of water by tube to 1 dog did not affect the level to which the blood urea nitrogen rises after the giving of blood by stomach tube. Neither did it affect the rate at which the peak is reached, nor did it alter the time required for the blood levels of urea nitrogen to return to normal.

As in all our other experiments, the hematocrit values and the specific gravity of the blood and plasma indicated no fluid shifts which could confuse the results.

It is concluded from a limited number (3) of experiments that forcing of water in doses

of 10 to 50 cc. per kilogram does not affect the level to which the blood urea nitrogen rises as a result of blood given in doses of 30 cc. per kilogram by stomach tube.

VIII. Effect of forcing water on the elevation of blood urea nitrogen associated with the low blood pressure caused by hemorrhage.

Comparison of the levels of blood urea nitrogen in table 4 with those in table 9 in dogs bled to reduce the blood pressure to comparable levels in both groups shows that the levels of blood urea nitrogen are definitely lower in the dogs bled and given water by tube than those of a group of dogs treated similarly except that water was restricted for the first twenty-four hours. It will be seen also that the urea clearance tends to remain higher at comparable blood pressures in the group given water.

Chart 1 presents these comparisons graphically. It can be noted from analysis of the curves that the blood pressures in the two groups are comparable and that not only do the levels of urea nitrogen fail to go as high in the dogs given water but they fall to normal a number of hours before they do in those dogs for which water was restricted for twenty-four hours.

In order to throw further light on the mechanisms involved, the blood urea nitrogen levels in the group given water and in the group not given water were correlated with the changes in the specific gravity of the blood and plasma.

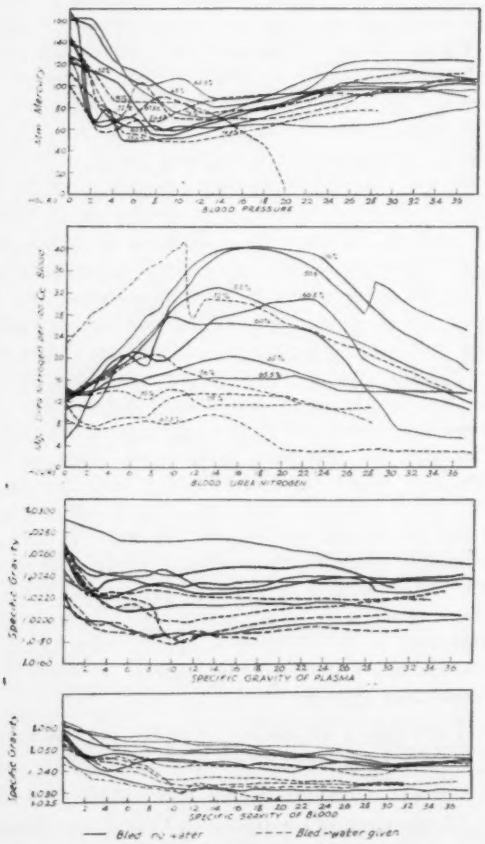

Chart 1.—Comparison of blood pressures, blood urea nitrogen levels and specific gravities of the blood and of the plasma of dogs which were bled and given water in the first twenty-four hours (broken lines) and of dogs bled and not given water (solid lines). Percentages in the upper graphs indicate the percentage of the total calculated blood volume removed.

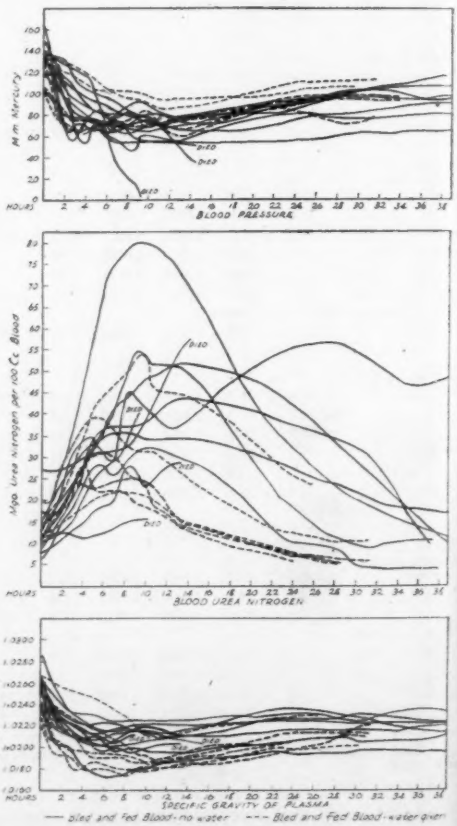

Chart 2.—Comparison of blood pressures, blood urea nitrogen levels and specific gravities of the plasma of dogs bled and fed blood to which water was given (broken lines) and of dogs to which water was not given (solid lines) in the first twenty-four hours.

It appears warranted to say that the blood urea nitrogen levels rise to significantly lower levels when the animals are given water. This

may be due to increased dilution of all body fluids or to better renal excretion.

IX. Effect of forcing of water on the elevation of blood urea nitrogen due to a combination of low blood pressure and feeding of blood.

Comparison of the results recorded in tables 5 and 10 show definitely that the level to which the blood urea nitrogen rises in dogs as a result of low blood pressure and feeding of blood is significantly less when water is given by stomach tube than when water is restricted. Study of the detailed figures for specific gravity of plasma in the two groups (with and without water) appears to show that there is no significant difference. It seems unlikely, therefore, that the lower levels of urea nitrogen in the group given water is due to a dilution effect of the plasma.

In general, the values for urea clearance in the two groups were higher in the group given water by stomach tube than they were in the group in which water was restricted. It is likely, then, that the giving of water was beneficial even when comparable blood pressures were obtained.

Chart 2 shows these comparisons more effectively graphically than do tables 5 and 10.

TABLE 8.—*Effect of Water by Stomach Tube on Urea Nitrogen After Feeding of 30 Cc./Kg. of Blood by Stomach Tube*

	Interval After First Bleeding		Water Given, Cc.	Fed Blood, Cc.	Blood Urea Nitrogen, Mg./100 Cc.	Hematocrit, per Cent	Specific Gravity		Blood Pressure, Mm. Hg	Urea Clearance, Cc./Min.
	Hr.	Min.					Blood	Plasma		
Dog 38 Weight, 11.6 Kg.			116							
Control			...	174	8.4	40.0	1.0533	1.0267	117	104.0
	2	15	...	174	15.4	42.0	1.0533	1.0264	...	....
	4	20	...	...	23.2	39.8	1.0526	1.0261	124	....
	6	7	...	...	34.4	39.0	1.0520	1.0253	...	....
	7	8	...	...	28.0	38.0	1.0498	1.0262	...	76.0
	8	9	...	...	23.8	36.0	1.0493	1.0259	...	....
	12	8	...	...	11.2	34.0	1.0480	1.0252	...	....
	19	50	...	...	4.2	37.0	1.0489	1.0263	...	....
	27	13	...	...	4.3	35.0	1.0489	1.0248	...	55.0
	31	20	...	...	4.4	31.0	1.0474	1.0246	...	....
	43	25	...	...	2.1	35.0	1.0509	1.0255	...	....
Dog 41 Weight, 9.3 Kg.			468							
Control			...	140	8.4	37.5	1.0516	1.0272	...	58.4
	2	28	...	140	21.0	36.0	1.0519	1.0276	...	....
	4	7	465	...	30.0	35.0	1.0523	1.0280	...	....
	5	15	...	...	32.9	37.0	1.0517	1.0280	...	....
	6	22	...	...	30.8	35.0	1.0498	1.0262	...	92.8
	7	23	...	...	25.5	35.0	1.0496	1.0267	...	....
	8	27	...	...	23.1	33.5	1.0486	1.0267	...	....
	14	9	...	...	11.9	35.0	1.0506	1.0276	...	....
	22	5	...	...	9.1	38.0	1.0528	1.0282	...	....
	28	45	...	...	9.1	38.5	1.0526	1.0282	...	....
	35	18	...	...	10.9	37.5	1.0524	1.0278	...	....
	46	5	...	...	12.4	39.5	1.0533	1.0279	...	....
Dog 40 Weight, 14.5 Kg.			145*							
Control			...	218	34.0	43.7	1.0545	1.0245	...	36.2
	2	10	...	210	36.4	42.0	1.0540	1.0238	...	....
	4	10	...	...	48.2	40.0	1.0540	1.0242	...	....
	5	42	...	...	51.7	42.0	1.0537	1.0243	...	....
	6	50	...	...	51.7	41.0	1.0528	1.0244	...	46.2
	7	40	...	...	35.5	39.8	1.0519	1.0232	...	....
	9	15	...	...	28.3	38.0	1.0410	1.0228	...	....
	12	40	...	...	18.9	34.4	1.0487	1.0225	...	....
	20	20	...	...	13.3	39.0	1.0524	1.0240	...	....
	27	8	...	...	18.9	39.6	1.0507	1.0242	...	....
	35	10	...	...	20.0	44.0	1.0567	1.0244	...	....
	44	40	.....	.....	18.2	42.0	1.0542	1.0237	...	....

It is concluded therefore that dehydration may be a factor in the extent to which blood urea nitrogen values rise as a result of feeding blood and of low blood pressures.

SUMMARY AND CONCLUSIONS

Azotemia associated with gastrointestinal hemorrhage was investigated by estimating the effects on the blood urea nitrogen of lowering

TABLE 9.—*Effect of Water by Stomach Tube on the Blood Urea Nitrogen in Dogs with Low Blood Pressure from Hemorrhage*

	Interval After First Bleeding		Water Given, Cc.	Bled, Cc.	Blood Urea Nitrogen, Mg./100 Cc.	Hematocrit, per Cent	Specific Gravity		Blood Pressure, Mm. Hg	Urea Clearance, Cc./Min.
	Hr.	Min.					Blood	Plasma		
Dog 37										
Weight, 11.1 Kg.			111							
Control			...	275	9.1	43.5	1.0542	1.0271	110	54.0
	2	5	...	174	7.4	34.8	1.0452	1.0236	88	....
	5	10	...	50	8.1	36.0	1.0463	1.0225	71	....
	6	27	...	...	8.4	36.0	1.0448	1.0223	...	....
	7	28	...	...	8.8	36.0	1.0457	1.0228	86	101.0
	8	29	...	100	8.1	36.0	1.0439	1.0228	89	....
	12	15	...	...	9.8	34.0	1.0420	1.0221	74	....
	20	10	...	(67.3%)*	3.5	31.0	1.0403	1.0219	81	....
	27	..	...	...	3.5	23.0	1.0352	1.0219	104	82.0
	31	45	...	...	3.2	23.0	1.0397	1.0218	110	....
	43	50	...	...	3.2	23.5	1.0399	1.0229	96	....
Dog 39										
Weight, 10.5 Kg.			105							
Control			...	250	22.4	44.7	1.0544	1.0268	126	15.5
	2	..	...	175	28.0	34.0	1.0459	1.0233	105	....
	4	3	...	50	30.8	27.0	1.0403	1.0212	65	....
	6	30	...	90	35.6	28.0	1.0399	1.0215	104	....
	9	9	...	42	38.4	21.4	1.0339	1.0199	72	....
	10	35	...	...	42.0	21.1	1.0325	1.0198	...	....
	11	41	...	(72%)*	27.0	19.5	1.0319	1.0199	...	4.2
	12	40	...	...	29.4	19.5	1.0324	1.0201	68	....
	20	15	...	...	26.6	19.0	1.0327	1.0211	70	....
	27	10	...	...	21.3	19.0	1.0314	1.0217	92	....
	35	3	...	...	14.7	15.0	1.0317	1.0226	102	....
	44	35	...	...	11.9	15.0	1.0338	1.0238	100	....
Dog 41										
Weight, 9.7 Kg.			485							
Control			...	250	14.0	42.0	1.0525	1.0246	140	22.9
	1	58	...	165	13.3	37.5	1.0475	1.0227	116	....
	3	59	...	100	14.0	35.5	1.0456	1.0224	86	....
	7	41	485	85	12.6	31.5	1.0421	1.0216	86	....
	9	50	485	100	14.7	22.5	1.0328	1.0183	...	....
	10	43	...	...	14.0	21.0	1.0296	1.0180	...	....
	11	50	...	(90%)*	12.6	26.0	1.0332	1.0189	78	33.1
	12	47	...	...	11.2	26.0	1.0332	1.0189	...	....
	14	10	...	...	11.9	23.5	1.0312	1.0185	62	....
	20	..	Died							
Dog 47										
Weight, 8.2 Kg.			82							
			82							
Control			...	200	12.4	31.0	1.0433	1.0212	100	35.0
	1	18	...	130	13.6	26.0	1.0403	1.0203	84	....
	2	37	...	...	15.6	25.5	1.0361	1.0194	58	....
	4	7	...	...	17.0	24.0	1.0355	1.0190	59	....
	5	34	82	40	19.1	23.0	1.0346	1.0189	66	....
	7	44	...	...	20.1	20.0	1.0329	1.0186	65	....
	8	54	82	(56.4%)*	20.4	20.0	1.0315	1.0188	...	30.3
	9	56	...	...	18.8	19.0	1.0306	1.0183	75	....
	12	15	...	...	16.4	17.0	1.0306	1.0187	85	....
	21	39	...	...	12.0	17.8	1.0310	1.0200	90	....
	27	57	...	...	11.0	16.0	1.0318	1.0203	90	....
Dog 49										
Weight, 6.3 Kg.			63							
			63							
Control			...	150	11.7	39.0	1.0509	1.0225	125	9.0
	1	10	...	100	8.4	38.0	1.0491	1.0212	120	....
	2	35	...	75	7.5	36.0	1.0455	1.0198	83	....
	4	45	...	...	8.9	33.0	1.0437	1.0197	58	....
	6	8	75	...	9.1	31.8	1.0415	1.0190	56	....
	7	37	...	75	9.1	30.0	1.0404	1.0186	83	....
	8	55	75	...	11.9	29.0	1.0361	1.0181	49	9.1
	9	52	...	(79.4%)*	12.6	27.5	1.0351	1.0179	53	....
	12	7	...	...	13.5	25.7	1.0354	1.0186	50	....
	22	13	...	...	12.0	20.8	1.0330	1.0198	71	....
	26	1	...	...	8.6	17.0	1.0312	1.0189	76	....

* Total per cent of calculated blood volume removed.

TABLE 10.—*Effect of Feeding Water on Blood Urea Nitrogen of Dogs Bled and Fed Blood*

	Interval After First Bleeding		Water Given, Cc.	Bled, Cc.	Blood Fed, Cc.	Blood Urea Nitrogen, Mg. per 100 Cc.	Hematocrit, per Cent	Specific Gravity		Blood Pressure, Mm. Hg	Urea Clearance, Cc./Min.
	Hr.	Min.						Blood	Plasma		
Dog 43 Weight, 9.5 Kg.											
			95								
			95								
	Control		...	200	143	10.8	36.5	1.0505	1.0266	130	25.4
	2	8	...	150	143	18.9	32.0	1.0480	1.0255	120	....
	4	50	95	95	...	30.1	28.5	1.0441	1.0248	104	....
	8	25	...	100	...	25.7	21.8	1.0363	1.0226	102	....
	9	30	...	...	...	23.9	20.0	1.0343	1.0212	...	....
	10	30	95	(72.7%)*	...	18.1	19.5	1.0343	1.0213	...	....
	11	33	...	...	...	16.7	20.5	1.0333	1.0209	95	30.0
	13	39	...	...	...	13.2	18.2	1.0335	1.0215	...	....
	23	20	...	...	...	6.3	17.6	1.0342	1.0228	102	....
Dog 44 Weight, 13.6 Kg.											
			136								
			136								
	Control		...	280	204	15.6	42.0	1.0557	1.0243	132	39.9
	2	2	...	200	204	22.5	40.0	1.0528	1.0231	128	....
	4	45	136	180	...	40.8	35.0	1.0479	1.0220	114	....
	8	26	...	145	...	51.2	28.5	1.0418	1.0200	95	....
	9	30	136	...	...	54.0	24.5	1.0366	1.0192	...	....
	10	25	...	(74%)*	...	46.6	24.5	1.0369	1.0191	...	....
	11	23	...	...	...	45.6	24.3	1.0355	1.0187	87	14.8
	13	23	...	...	...	44.6	24.8	1.0365	1.0193	...	....
	23	7	...	...	...	27.3	21.8	1.0354	1.0204	109	....
Dog 45 Weight, 5.9 Kg.											
			59								
			59								
	Control		...	150	89	14.8	46.0	1.0564	1.0241	138	28.5
	1	1	...	100	...	17.2	41.5	1.0584	1.0210	128	....
	2	7	...	70	89	22.2	35.0	1.0445	1.0194	90	....
	3	4	...	...	...	24.5	31.0	1.0413	1.0179	62	....
	4	45	59	50	...	22.6	29.5	1.0404	1.0186	84	....
	8	18	...	...	...	25.0	24.5	1.0341	1.0178	68	....
	9	32	59	(78%)*	...	24.5	23.0	1.0333	1.0178	...	28.3
	10	25	...	...	...	23.6	21.8	1.0325	1.0178	72	....
	12	42	...	...	...	16.1	20.0	1.0325	1.0183	66	....
	22	32	...	...	...	7.7	18.0	1.0335	1.0204	88	....
	29	15	...	...	...	5.6	16.5	1.0329	1.0215	95	....
Dog 46 Weight, 8.0 Kg.											
			80								
			80								
	Control		...	200	120	19.8	36.0	1.0486	1.0229	128	34.4
	0	52	...	130	...	19.2	32.0	1.0449	1.0208	100	....
	1	58	...	50	120	26.8	30.5	1.0414	1.0205	72	....
	2	41	...	...	...	32.0	28.0	1.0347	1.0199	66	....
	4	51	80	30	...	39.5	24.5	1.0363	1.0195	71	....
	8	8	...	50	...	32.4	20.4	1.0329	1.0192	83	....
	9	12	...	30	...	31.7	19.0	1.0317	1.0190	70	....
	10	9	...	...	...	31.7	Clot	1.0279	1.0184	68	22.3
	12	17	...	(76.5%)*	...	27.7	16.8	1.0280	1.0187	73	....
	22	10	...	...	...	12.6	16.0	1.0309	1.0202	89	....
	28	50	...	...	...	10.1	15.0	1.0315	1.0209	92	....
Dog 48 Weight, 7.3 Kg.											
			73								
			73								
	Control		...	175	110	17.5	35.0	1.0459	1.0221	106	26.7
	1	19	...	75	...	15.8	24.4	1.0377	1.0193	77	....
	2	33	...	50	110	19.0	24.0	1.0339	1.0192	70	....
	3	57	...	...	...	27.8	20.0	1.0311	1.0181	66	....
	5	28	73	50	...	22.1	19.5	1.0311	1.0180	75	....
	7	41	...	...	...	22.4	16.5	1.0283	1.0175	64	....
	8	56	73	(60%)*	...	19.7	16.3	1.0284	1.0180	...	22.7
	9	51	...	...	...	18.4	14.5	1.0272	1.0180	66	....
	12	6	...	...	...	15.1	13.5	1.0275	1.0181	76	....
	21	45	...	...	...	8.5	15.7	1.0292	1.0197	86	....
	27	47	...	...	...	5.5	14.0	1.0292	1.0198	76	....
Dog 50 Weight, 7.2 Kg.											
			72								
			72								
	Control		...	175	108	11.9	35.3	1.0482	1.0243	106	10.8
	1	10	...	115	...	13.5	28.0	1.0417	1.0220	96	....
	2	30	...	80	108	16.1	28.3	1.0404	1.0210	78	....
	4	47	...	50	...	19.7	20.0	1.0325	1.0192	74	....
	5	57	72	...	...	21.3	19.2	1.0316	1.0192	62	....
	7	39	...	50	...	22.2	18.0	1.0305	1.0190	74	....
	8	48	72	...	...	21.8	17.8	1.0291	1.0187	...	....
	9	47	...	(81.5%)*	...	21.6	17.0	1.0284	1.0186	83	7.0
	12	2	...	...	...	17.2	15.0	1.0281	1.0187	59	....
	22	3	...	...	...	8.6	14.0	1.0299	1.0212	98	....
	27	49	...	...	...	5.5	13.0	1.0299	1.0214	96	....

* Total per cent of calculated blood volume removed.

blood pressure by bleeding, of feeding dog's blood by stomach tube, of anemia, of withholding water and of combinations of these in sixty-two experiments on dogs.

Systolic blood pressures of 70 to 80 mm. of mercury resulted in rises of blood urea nitrogen to 25 to 40 mg. per hundred cubic centimeters. Blood by stomach tube raised the blood urea nitrogen levels to 25 to 30 mg. per hundred cubic centimeters. The rise and fall of blood urea nitrogen due to ingested blood was faster than that due to low blood pressure. Severe anemia due to hemorrhage did not produce azotemia. Combined effects of low blood pressure and blood by stomach tube produced rapid rises of blood urea nitrogen characteristic of the latter, rises of longer duration characteristic of the former and higher levels than one would expect from either alone.

Urea clearance was not diminished in dogs given blood by stomach tube. Falls in urea clearance occurred in every dog in which there were a significant fall in blood pressure and an elevation of blood urea nitrogen. Values of urea clearance and blood urea nitrogen in dogs with different intakes of water indicate that dehydration may contribute to azotemia associated with gastrointestinal bleeding.

Azotemia associated with gastrointestinal bleeding may be due to decreased renal function caused by low blood pressure and dehydration or to absorption of digested blood proteins. Anemia is not a factor. Absorption of digested blood from the gastrointestinal tract does not decrease renal function.

APLASTIC ANEMIA AND ITS ASSOCIATION WITH HEMOCHROMATOSIS

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Although hemochromatosis is a comparatively rare condition, its association with aplastic anemia is frequent enough to suggest that the combination of the two diseases is more than accidental. The purpose of this paper is to draw further attention to this association by reviewing the reported cases, adding another case and discussing the pathologic changes common to the two conditions.

Whitby and Britton [1] stated that about 150 cases of idiopathic aplastic anemia are recorded in the literature on medicine. Thompson, Richter and Edsall [2] and later Rhoads and Miller [3] drew attention to the discrepancy between the peripheral blood and the bone marrow and to the frequent occurrence of cellular and even hypercellular marrow when the elements in the peripheral blood were reduced in numbers. Rosenthal [4] distinguished between two forms of aplastic anemia, the typical and the atypical. The atypical form includes the chronic type of aplastic anemia with cellular marrow, also called pseudoaplastic anemia. Bomford and Rhoads [5] suggested that until a classification based on causation is available the term refractory anemia be used for every anemia which fails to respond to any form of treatment except transfusions of blood. Israëls and Wilkinson [6] described the syndrome of achrestic anemia as different from aplastic anemia, but this separation has not been accepted by other investigators.[7]

In a study of 66 patients with refractory anemia, Bomford and Rhoads [5] subdivided their cases into four groups according to the findings in the bone marrow. In 9 of 31 patients with refractory anemia characterized by partly mature cellular marrow, corresponding to the pseudoaplastic anemia described by other observers, a varying degree of pigmentation of the skin developed in the course of several years. In 3 patients with marked pigmentation, 1 of whom had diabetes, autopsy revealed the lesions of hemochromatosis. Kark [8] and Mackey [9] each reported an instance of chronic aplastic anemia complicated by hemochromatosis. No autopsy was done in Kark's case, so the diagnosis could not be confirmed except insofar as examination of a piece of excised skin showed changes that were said to be characteristic. The case of a patient with cirrhosis of the liver and pernicious anemia who after satisfactory response to liver therapy became hypersensitive to liver was reported by Markoff.[10] Pigmentation of the skin developed, and the patient died because of anemia which was refractory to liver therapy and because of

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uncontrollable bleeding. The presence of hemochromatosis was confirmed at autopsy. However, studies of the bone marrow showed the changes of pernicious anemia, and for this reason the case is not included in our series. Other workers,[11] who reviewed larger numbers of cases of aplastic anemia, did not state that either pigmentation of the skin or hemochromatosis was revealed at autopsy.

Sheldon,[12] in his monograph reviewing the literature on hemochromatosis up to 1935, stated that "the blood picture is normal except for a slight degree of anemia which is by no means constant, and is no more than is to be expected in the terminal stages of any chronic disease." Naegeli[13] mentioned the occasional occurrence of anemia in hemochromatosis. Butt and Wilder[14] described the cases of 30 patients for whom a diagnosis of hemochromatosis was made during life. These authors found an average of 3,990,000 red blood cells per cubic millimeter, with slight macrocytosis in 3 patients. Wintrobe and Shumacker's and Wintrobe's papers[15] mentioned 1 case of their own and 4 in the literature in which pigmentary cirrhosis was present with macrocytic anemia. A case of pernicious anemia associated with hemochromatosis was reported by Roth[16] and by Cain.[17] R. R. Kracke, discussing Cain's paper,[17] mentioned a patient with macrocytic anemia, hepatomegaly and splenomegaly, without glycosuria and without abnormal pigmentation of the skin, who at autopsy presented the visceral changes of hemochromatosis. No further details of the autopsy or of the blood picture were given. In Meader's case[18] immature forms of erythrocytes and granulocytes were present in the peripheral blood. Even from this short review it is apparent that anemia is not a feature of hemochromatosis and that if present it is due to complicating conditions.

REPORT OF A CASE

P. B., a 65 year old white American of German extraction, was admitted to Goldwater Memorial Hospital on Sept. 22, 1943. He complained of weakness, shortness of breath and swelling of the legs.

History.—The patient had been a structural engineer until 1929. Since then he had worked as a laborer. There was no available evidence of exposure to hemotoxic agents. He had consumed large amounts of alcohol in his youth, but his intake for the past thirty years had been moderate. None of his family was known to have suffered from any disease of the blood. There was nothing in his history which could be considered relevant to his present condition.

Approximately five years prior to the patient's first admission to the hospital his marked pallor had been commented on by his wife and his friends, but he felt well and did not seek medical attention. In December 1942, weakness, dyspnea on exertion and edema of the region of the ankles necessitated hospitalization. During the following seven months he was readmitted to the hospital five times for blood transfusions. In April 1943 he was readmitted because of congestive heart failure and was given maintenance doses of digitalis and mercurial diuretics.

The patient stated that he had lost 30 pounds (13.6 Kg.) since 1940. There was no history of dyspepsia, burning of the tongue, dysphagia, tendency to bleed or to bruise easily or paresthesias. He was hospitalized in another institution from July to September 1943, when he was transferred to Goldwater Memorial Hospital. Treatment in both hospitals consisted of intramuscular administration of large quantities of liver extract, iron and vitamins and transfusions of blood.

Physical Examination.—At the time of his admission to the hospital the patient appeared well developed but chronically ill. He was not dyspneic. There was evidence of recent loss of weight. The skin and the visible mucous membranes were strikingly pale, with a suggestion of an icteric tint. On the left forearm two ecchymoses, approximately 1 cm. in diameter, were present, and many irregularly shaped dark brown-pigmented areas were visible over the dorsa of the hands and on the forearms. No other signs of pigmentation were noted. There were no detectable enlargements of the lymph nodes. The eyelids were slightly edematous. The scleras were lemon yellow. The fundi were not pale. There were old small retinal hemorrhages in the right eye. Slight atrophy of the lateral borders of the tongue was noted. Engorgement of the veins of the neck was observed, and arterial pulsations were seen in the supraclavicular spaces. There were a few moist rales over the base of each lung. The heart was enlarged to the left. The sounds were of good quality, with a soft systolic murmur at the apex transmitted toward the base. The blood pressure was 150 mm. of mercury systolic and 50 diastolic. The liver was palpable 9 cm. below the costal margin in the midclavicular line; it was firm and nontender, and the edge was sharp. The spleen was palpable 2 cm. below the left costal

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margin and was firm and not tender. No fluid wave or shifting dulness was present. The genitalia were normal except for edema of the scrotum. There was pitting edema of the lower extremities. Koilonychia was not seen. The reflexes were normal. There were no sensory disturbances, and the senses of vibration and position were normal.

Laboratory Data.—Urine: The urine was concentrated to 1.024. It gave negative reactions to tests for albumin and sugar and (in a dilution of 1:10) to the test for urobilinogen. Tests for bile and for Bence Jones protein also gave negative results. Examination of the urinary sediment revealed no abnormal changes. The results of the phenolsulfonphthalein test were as follows: first hour, excretion of 30 per cent of the dye; second hour, excretion of 10 per cent.

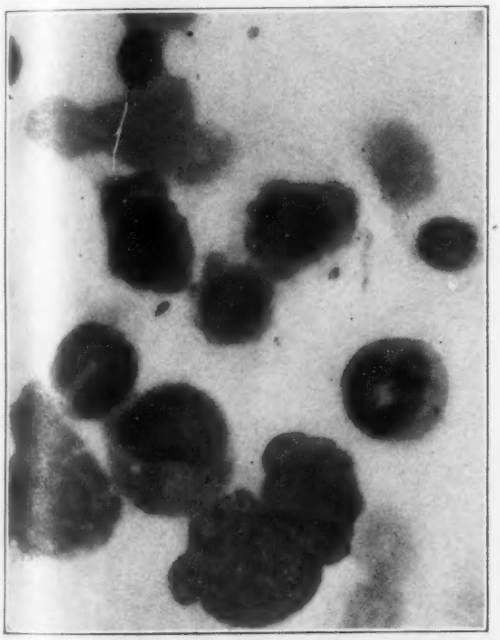

Fig. 1.—Smear of sternal marrow showing normoblasts in different stages of development. The cell in the lower left corner represents the earliest normoblast in the field. The cell placed next to it for comparison is a myelocyte. The cell below the myelocyte is a pronormoblast. Wright's stain; × 1,600.

Blood: The fasting level of the blood sugar on two occasions was 110 mg. and 130 mg. respectively per hundred cubic centimeters. The dextrose tolerance test showed a fasting level of 118 mg. per hundred cubic centimeters of blood; one hour after administration of 100 Gm. of dextrose, 214 mg., and two hours after administration of dextrose, 167 mg. (Dextrose was absent from the urine throughout this test.) The blood contained 34 mg. of nonprotein nitrogen per hundred cubic centimeters. It showed 4.3 mg. of uric acid, 8.9 mg. of calcium and 4.6 mg. of phosphorus per hundred cubic centimeters. The serum contained 1.4 Bodansky units of alkaline phosphatase and 114 mg. of cholesterol (51.4 mg. as esters) per hundred cubic centimeters. The total protein was 5.6 Gm., the albumin 3.98 Gm. and the globulin 1.69 Gm., per hundred cubic centimeters. The sulfobromophthalein sodium test (5 mg., per kilogram of body weight) showed retention of 7.5 per cent of the dye after thirty minutes and no retention after forty-five minutes. The cephalin flocculation test gave negative results. The prothrombin time, determined with diluted plasma (12.5 per cent), was seventy seconds (normal, thirty-seven to forty-two seconds). With daily parenteral administration of 6 mg. of menadione in corn oil the prothrombin time decreased to sixty-one seconds on the sixth and seventh days and increased to seventy-five seconds on the ninth and tenth days. In the congo red test 77.4 per cent of the dye was left in the blood after one hour. The icterus index was 4.5 and 4 units. The van den Bergh direct test gave negative results; the indirect showed a slight trace of bilirubin. The Kahn and Kline reactions of the blood were negative.

On the patient's admission to the hospital there were 1,400,000 red blood cells, 4,900 white blood cells and 216,000 platelets per cubic millimeter; the hemoglobin content was 36 per cent and the reticulocytes amounted to 3.1 per cent. The mean corpuscular volume was 100 cubic microns, the mean corpuscular hemoglobin 33 micromicrograms and the mean corpuscular hemoglobin content 33 per cent. The color index was 1.1. The differential count was as follows: polymorphonuclear cells 48 per cent, stab cells 14 per cent, eosinophils 2 per cent, basophils 1 per cent, monocytes 3 per cent and lymphocytes 32 per cent. The red cells showed marked anisocytosis and poikilocytosis. Many macrocytes were seen. Polychromatophilic and large basophilic stippled red cells were rare. Two normoblasts per hundred white blood cells were counted. The bleeding time, the coagulation time and the reaction to the Rumpel-Leeds test were normal. The result of a test of the red cells for fragility gave results within normal limits.

During the patient's stay in the hospital his red cell counts varied between 1,150,000 and 2,500,000, his hemoglobin between 34 per cent and 54 per cent and his white blood counts between 2,600 and 6,100. The reticulocyte count decreased to below 1 per cent during the last two months.

Bone Marrow: An aspiration of the bone marrow was done on Oct. 27, 1943. The smears were very cellular. There was an increase in the percentage of nucleated red cells, with basophilic and polychromatic normoblasts predominating (fig. 1). The number of mature granulocytes was markedly diminished. Hemosiderin was present in the reticulum cells, the number of which was increased.

The following tabulation summarizes the differential count of the cells of the bone marrow:

	Per Cent		Per Cent
Myeloblasts	2.0	Polymorphonuclear cells, neutrophilic	1.8
Promyelocytes	2.2	Lymphocytes	4.8
Myelocytes:		Reticulum cells....	3.4
Neutrophilic	4.6	Undifferentiated cells	0.6
Eosinophilic	0.6	Pronormoblasts ...	2.0
Metamyelocytes:		Normoblasts:	
Neutrophilic	6.2	Basophilic	18.2
Eosinophilic	0.6	Polychromatic...	26.0
Stab forms:		Orthochromatic..	8.8
Neutrophilic	18.0		
Eosinophilic	0.2		

Stomach: On gastric analysis free hydrochloric acid was found in a fasting specimen and in all specimens after administration of alcohol.

Stool: No ova, parasites or occult blood were demonstrated in the stool.

Roentgen Findings (Reported by Dr. Henry K. Taylor).—The lungs were normal except for a moderate degree of emphysema. The heart was enlarged, and the configuration was of a hypertensive type.

There was no increase in the density of the liver.

There was no evidence of osteosclerosis of the skull, spine, pelvis or lower extremities. The middle third of the tibias showed an increase in the thickness of the cortex, with no encroachment on the medullary canals. The lumbar portion of the spine showed productive changes in the bone. The cranial vault was normal in thickness. The diploic layer was barely perceptible. The density of the vault was probably greater than the average, but was insufficient to be considered evidence of osteosclerosis. There were calcific deposits in the choroid plexus. The sella turcica showed nothing abnormal. There were irregular areas of calcification in the pituitary fossa.

Roentgenograms of the skull, the femurs and the alimentary canal made at another hospital revealed no additional information; the calcific deposits in the choroid plexus and in the pituitary fossa were noted also.

In view of the large amounts of iron pigment found in the various organs at autopsy, it is possible that the radiopaque densities considered as calcific deposits in the choroid plexus and in the pituitary fossa were due to incrustations of iron. However, since permission for necropsy did not include the brain, this hypothesis could not be confirmed.

Electrocardiographic Findings.—The electrocardiogram showed normal sinus rhythm with occasional premature auricular contractions. There was deviation of the electrical axis to the left and left bundle branch block of the discordant type.

Course in the Hospital.—The patient's temperature rose occasionally to as high as 100 F. He offered no complaints except as to swelling of the legs and weakness; the latter condition improved after transfusions. He was ambulatory. He received intensive parenteral liver therapy, iron and copper, brewer's yeast and a diet high in calories. The peripheral edema was controlled with digitalis and mercurial diuretics. Transfusions of blood, some of which were followed by slight chills and elevation of temperature as high as 104 F., were necessary every three to four weeks. During the last weeks of the patient's life transfusions were given more often. Their effect, however, became short lived; edema and weakness increased, and after three months in the hospital the patient died, on Dec. 29, 1943.

Necropsy.—Autopsy was performed ninety-seven hours after death. The permission for autopsy did not include examination of the brain.

Gross Examination: The body was well nourished. The skin was pale and slightly yellowish. The scleras were subicteric. The skin of the forearms and the dorsa of the hands was gray-brown. The jaws were edentulous, and the mucous membrane of the mouth was free from pigment. The tongue showed no atrophy. The thyroid gland was enlarged and well encapsulated and showed many yellowish cystic areas. The chest was barrel shaped; the lungs, emphysematous. Both ventricles of the heart were hypertrophied and dilated, the right proportionately more than the left. The myocardium was red-brown and showed slight fibrosis. The hepatic, mesenteric, renal, splenic and iliac vessels were free of thrombi, as was the portal vein.

The abdomen contained no free fluid. The liver was enormous, weighing 3,050 Gm.; it reached to within 3 cm. of the left axillary line at the level of the fifth rib. On the right it extended 8 cm. below the costal margin. Its color was a striking orange-brown. The capsule was thickened and irregularly opaque and contained numbers of petechial hemorrhages. The surface was finely nodular. On section the organ was extremely firm and gritty, and the color was uniform. Small irregular nodules outlined by gray-white streaks could be seen throughout the substance of the liver.

The gallbladder contained two soft concrements but was otherwise normal.

The pancreas was firm and of a lighter orange-brown tint than the liver. The lobular architecture was normal.

The spleen weighed 250 Gm. The capsule was slightly thickened. On section the organ was firm and dark red. The fibrous markings were increased.

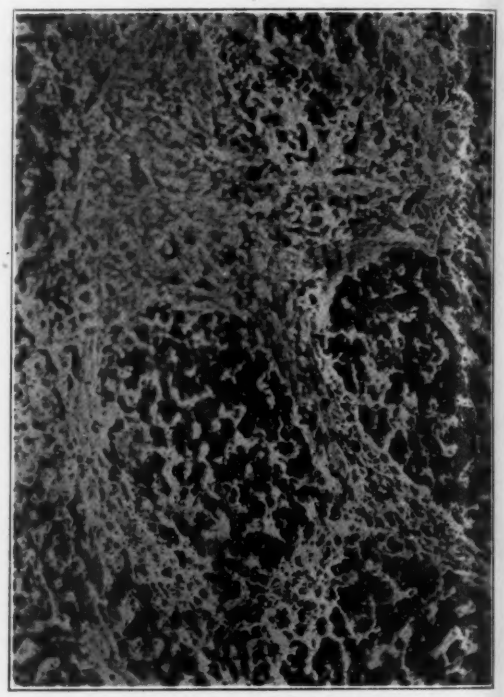

Fig. 2.—Periportal fibrosis dividing the liver into nodules. Even at this low magnification granules of dark pigment can be seen in the cytoplasm of some of the parenchymal cells. Masson's trichrome stain; × 100.

The esophagus did not contain varices. There was no abnormal pigmentation throughout the stomach and intestines.

The kidneys showed slight cortical scarring and were of normal size and color.

The adrenal glands appeared to be normal.

The hilar and mediastinal lymph nodes were anthracotic. The periaortic nodes were mottled rust and gray, while those of the peripancreatic and perihepatic regions were almost uniformly rust colored. They were all enlarged in varying degrees.

The ribs, the sternum and the vertebrae showed gray-red marrow. The cortex of these bones was not thickened.

There was edema of the lower part of the right leg but no abnormal pigmentation.

Microscopic Examination: The following findings were noteworthy in the present connection: Small amounts of pigment were scattered through the alveoli of the lungs. Some of the pigment gave a positive reaction to stains for iron. Slightly larger amounts of perinuclear pigment in the heart muscle gave a similar reaction; in addition, there was the usual amount of unstained lipochrome. There was no demonstrable hemosiderin in the areas of fibrosis.

The liver was divided into irregular nodules by bands of fibrous tissue (fig. 2). The parenchymal cells were

Fig. 3.—Acinar cells of the pancreas. Pigment granules appear black and in some cells are so densely clumped as to be indistinguishable from the nuclei. The connective tissue is increased. Iron stain; × 772.

loaded with brown refractile pigment, much of which became blue with stains for iron. The most heavily laden cells were those about the portal areas. Many of the cells that were overcrowded with pigment seemed to be disintegrating. The Kupffer as well as the parenchymal cells were similarly affected. The periportal fibrous tissue was increased and contained large clumps of intracellular and extracellular hemosiderin and unstained brown pigment. The epithelial cells of the bile ducts were likewise pigmented. There was moderate proliferation of small bile ducts but little apparent regeneration of parenchymal cells. In addition to these changes there were thickening of the central vein and disintegration of the cells of the liver in the vicinity. There were moderate numbers of areas of extramedullary hemopoiesis.

The pancreas showed large amounts of hemosiderin in the acinar cells (fig. 3) as well as in the epithelium of the ducts. There was increase in fibrous tissue, and in it were clumps of iron-containing pigment. The islets were large and were frequently surrounded by fibrous tissue. A moderate amount of iron pigment was present in the islet cells. The parenchyma and the islets had undergone rather severe autolysis (fig. 4). However, it seemed that most of the pigmented cells in the islets were still fairly well preserved, while those of the acinar tissue were necrotic. Phagocytes with granules of pigment were also demonstrable.

Sections of the spleen showed chronic passive congestion with a few small islands of extramedullary hemopoiesis. Stains for iron confirmed the observation made in sections stained with hematoxylin and eosin that there was a small amount of diffusely scattered iron-containing pigment.

The cortex of the adrenal glands and the epithelial cells of the thyroid and prostate glands also contained hemosiderin.

Unfortunately, no sections of the testis, the gastrointestinal tract or the skin were available.

The lymph nodes were large. They contained hemosiderin. The perihepatic and peripancreatic nodes were most heavily burdened, while the mediastinal nodes contained only small amounts. Again there was little extramedullary hemopoiesis.

In sections from the ribs, the sternum and the vertebrae stained with hematoxylin and eosin and with Giemsa's stain the marrow cells were mainly of the erythropoietic type. Their number was increased at the expense of fat. Their number was about equally divided between stem cells and pronormoblasts, with fewer normoblasts. There was also a moderate number of mature red cells. There was depression of the white blood cell series. Only an occasional mature polymorphonuclear cell was visible. Megakaryocytes were

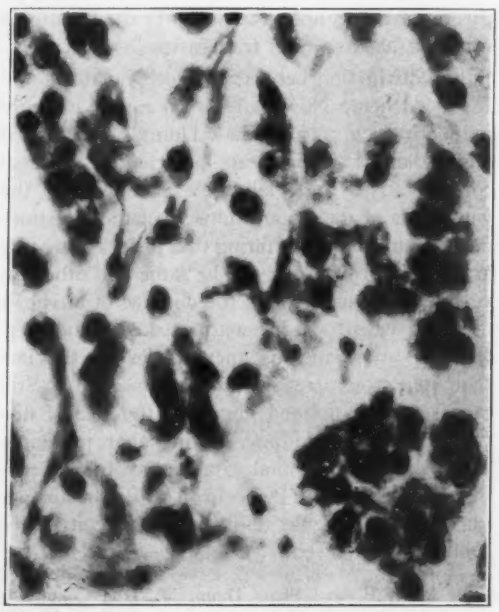

Fig. 4.—Islet cells of the pancreas. Pigment visible as dark granules in the cytoplasm of the cells. Iron stain; × 772.

seen in decreased numbers. The cortex and the periosteum were not unusual.

The bone marrow as seen at autopsy showed, when compared with that in the smear from the sternum taken in October 1943, regression toward a more immature state. The stem cells were extremely pale, large, basophilic and poor in chromatin. The pronormoblasts were smaller, with clearly differentiated nuclei and one or more nucleoli. The more mature normo-

blasts were about the size of lymphocytes, with dense "clock face" nuclei and rims of basophilic cytoplasm.

The kidneys showed mild cortical scarring. Pigmentation was present but was confined almost exclusively to the epithelium of the ascending loops of Henle and to the cells of the distal convoluted tubules.

The amount of fibrous tissue in the liver of this patient with anemia, while not as great as that in the liver of the average person with idiopathic hemochromatosis, was extensive enough to warrant the diagnosis of portal cirrhosis. The amount of fibrous tissue and pigment that was demonstrated in the pancreas was even greater than that in the average patient with hemochromatosis, while the spleen showed less iron pigment.

Stains of the bone marrow for iron showed less hemosiderin than is seen in the average patient with hemochromatosis.

Anatomic diagnoses included: pseudoaplastic anemia of unknown origin, extramedullary hemopoiesis (mild), hemochromatosis, portal cirrhosis, hepatosplenomegaly, coronary sclerosis, cardiac hypertrophy and dilatation, myocardial fibrosis, pulmonary emphysema and fibrosis, pyelitis cystica, edema of the right lower extremity and nodular hyperplasia of the thyroid gland.

COMMENT

The significance of the coexistence of hemochromatosis and aplastic anemia in the 6 patients who had had repeated transfusions is obscure.

The distinction between hemochromatosis and advanced hemosiderosis rests on rather insecure foundations. Muir and Shaw Dunn [19] emphasized pigmentation of the heart muscle, the adrenal cortex, the thyroid gland, the ependyma of the ventricle and the smooth muscle of the intestines in hemochromatosis, stating that it does not occur as a result of hemolysis. The same and other investigators [20] have noted the absence of cirrhosis of the liver in persons with marked hemosiderosis due to pernicious anemia, despite the fact that numerous transfusions were given. Still others [21] have pointed out the difference of distribution in the kidney, stating that in hemosiderosis the proximal convoluted tubules are affected, whereas in hemochromatosis the ascending loops of Henle and the distal convoluted tubules are involved.

Rous and Oliver [22] attempted to produce hemochromatosis by giving transfusions of 10 to 15 cc. of blood to rabbits daily for periods up to six and one-half months. In addition to large amounts of hemosiderin in the liver, they found deposits in the adrenal cortex, the submaxillary glands, the cartilages of the trachea, and the skin and large deposits in the kidneys. The pancreas was affected only in animals subjected to this procedure for a considerable length of time and then only slightly. Furthermore, the kidneys held heavy deposits in contrast to the sparse pigmentation in hemochromatosis. No pigment was found in the thyroid gland. These workers noted cirrhosis of the liver in 2 of the 3 rabbits but felt that it was an unrelated finding.

Hueck [23] emphasized the sparse distribution of hemosiderin in the spleen, the bone marrow and the kidneys in hemochromatosis in contrast to the abundant pigmentation of these organs in hemosiderosis. He expressed the opinion that the presence or the absence of hemofuscin is an important point for purposes of differentiation. However, there are two theoretic objections to this concept:

1. Much of the "iron-free" pigment in hemochromatosis is found to contain iron when subjected to careful technic, and therefore the amount of hemofuscin varies.

2. In the present state of knowledge of the composition of hemofuscin, we see no reason why it should not exist in hemosiderosis.

There are many writers, principally of the French school,[24] who do not make any distinction between hemochromatosis and hemosiderosis. An excellent discussion of the subject is presented by Sheldon,[12] who concluded that there are differences in distribution in the spleen, the bone marrow and the kidneys but maintained that a certain similarity exists, since the body tends to distribute hemosiderin by a common mechanism, whatever the source of the iron.

Whipple and Bradford,[25] in reporting 8 cases of Cooley's anemia, noted the distribution and

19. Muir, R., and Shaw Dunn, J.: Iron Content of Organs in Bronzed Diabetes, J. Path. & Bact. **19**:226, 1914.

20. (*a*) Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1943. (*b*) Whitby and Britton.[1] (*c*) Yates, J. L., and Thalhimer, W.: Treatment of Pernicious Anemia (A Patient Who Received 113 Transfusions), J. A. M. A. **87**:2156 (Dec. 25) 1926. (*d*) Jones, H. W.: Prolonged Blood Transfusions in Pernicious Anemia, ibid. **86**:1673 (May 29) 1926.

21. Gaskell, J. F.; Mackenzie Wallis, R. L.; Sladden, A. F.; Vaile, P. T., and Garrod, A. E.: Contribution to the Study of Bronzed Diabetes, Quart. J. Med. **7**: 129 (Jan.) 1914.

22. Rous, P., and Oliver, J.: Experimental Hemochromatosis, J. Exper. Med. **28**:629 (Nov.) 1918.

23. Hueck, W.: Haemochromatose, in Krehl, L., and Marchand, F.: Handbuch der allgemeinen Pathologie, Leipzig, S. Hirzel, 1921, vol. 3, pt. 2, p. 371.

24. Roque, G.; Chalier, J., and Nové-Josserand, L.: Étude critique sur la conception des cirrhoses pigmentaires: Origine hémolytique de leur siderose, Rev. de méd., Paris **33**:353 (May) 1913.

25. Whipple, G. H., and Bradford, W. L.: Racial or Familial Anemia of Children Associated with Fundamental Disturbances of Bone and Pigment Metabolism (Cooley-von Jaksch), Am. J. Dis. Child. **44**:336 (Aug.) 1932; Mediterranean Disease-Thalassemia (Erythroblastic Anemia of Cooley), J. Pediat. **7**: 279 (Sept.) 1936.

types of pigment and concluded that they were similar to those of hemochromatosis. However, these writers did not find an accompanying cirrhosis of the liver.

From experimental and pathologic evidence, the anatomic basis for a diagnosis of hemochromatosis as opposed to hemosiderosis rests on the following criteria:

1. The presence in hemochromatosis of portal cirrhosis in addition to large amounts of hemosiderin in the liver.

should be a high incidence of hemochromatosis in the hemolytic and pernicious anemias. That this is not true is shown by numerous reports in the literature [26] on these diseases. Secondly, one should be able to reproduce hemochromatosis experimentally by repeated transfusions,[22] by hemolytic agents [27] and by injections of hemoglobin [28] and of dialyzed iron.[29] Such attempts have been unsuccessful. Finally, that the availability of iron stored in the liver for synthesis of hemoglobin differs in hemochromatosis and in

Principal Features of Reported Cases of Aplastic Anemia Associated with Hemochromatosis

Author	Age at Onset, Sex	Duration, Yr.	Age at Death, Yr.	Blood Counts on Admission	Amount of Transfused Blood	Diabetes	Bone Marrow	Summary of Autopsy
Kar[illegible], R. M.	30 ♂	10	40	RBC: 2,500,000 Hb: 50% CI: 1 WBC: 3,500	290 transfusions in 9 years	Hyperglycemia; no glycosuria	No aplasia; cellular	No autopsy; pigmentation of skin (biopsy) conjunctivas and teeth; enlargement of liver
M[illegible]y, R.	46 ♂	3½	49½	RBC: 1,050,000 Hb: 22% CI: 1.08 WBC: 4,100	39.8 liters	Not mentioned	Selective aplasia of erythropoiesis	Pigmentation of lymph nodes, pancreas and heart muscle; fibrosis and pigmentation of liver
Bo[illegible]ford, R. R. and Rh[illegible]s, C. P.	51 ♂	2½	53½	RBC: 1,400,000 Hb: 30% CI: 1.07 MCV: 90 cu.μ Retic: 1.4% WBC: 1,150 Platelets: 68,000	16 transfusions	Not present	Cellular	Pigmentation of skin and lymph nodes; fibrosis and pigmentation of liver and pancreas
	68 ♂	2	70	RBC: 1,300,000 Hb: 35% CI: 1.3 MCV: 104 cu.μ Retic: 1.4% WBC: 4,350	12 transfusions	Not present	Cellular	Pigmentation of skin, lymph nodes, adrenal glands and choroid plexus; fibrosis and pigmentation of liver and pancreas
	12 ♂	9	21	RBC: 1,300,000 Hb: 26% CI: 1 MCV: 86 cu.μ Retic: 0.4% WBC: 3,850 Platelets: 60,000	54 transfusions	Glycosuria	Cellular	Pigmentation of skin, lymph nodes, adrenal glands and cardiac muscle; fibrosis and pigmentation of liver and pancreas
Authors' case	64 ♂	1	65	RBC: 1,500,000 Hb: 35% CI: 1.2 MCV: 100 cu.μ Retic: 3.1% WBC: 4,900 Platelets: 216,000	12.8 liters, 17 transfusions	Hyperglycemia; no glycosuria	Cellular	Pigmentation of skin, lymph nodes, adrenal glands, kidneys, heart muscle, lungs and thyroid and prostate glands; fibrosis and pigmentation of liver and pancreas

2. Increased fibrous tissue in the pancreas with deposits of pigment in the islet cells as well as in acinar cells and the epithelium of the ducts.

3. The relatively small amount of pigment in the kidneys, the spleen and the bone marrow.

The case reported here fulfilled all these requirements and, in addition, presented, clinically, an elevated curve of tolerance for dextrose, signifying pancreatic damage.

We believe that intense hemosiderosis is an entity. If hemochromatosis and hemosiderosis were different degrees of the same process, there

hemosiderosis is seen from the experiments of Muir and Shaw Dunn [30] and of Whipple and his

26. Whitby and Britton.[1] Wintrobe.[20a]

27. Muir, R., and Shaw Dunn, J.: Retention of Iron in Organs in Haemolytic Anaemia, J. Path. & Bact. **19**:417, 1914.

28. Muir, R., and Young, J. S.: Relation of the Liver to the Disposal of Haemoglobin, J. Path. & Bact. **35**:113 (Jan.) 1932.

29. Polson, C. J.: The Fate of Colloidal Iron Administered Intravenously: Long Experiments, J. Path. & Bact. **32**:247 (April) 1929.

30. Muir, R., and Shaw Dunn, J.: Absorption of Iron from the Organs After Haemolysis, ibid. **20**:41, 1915.

co-workers.[31] It is therefore unlikely that transfusions in a patient with pseudoaplastic anemia could be responsible for hemochromatosis.

In the accompanying table the essential features of the reported cases of aplastic anemia associated with hemochromatosis are given. With the exception of the patient in the third case, who lived above a garage and complained of the odor of fumes, no patient gave a history of exposure to potentially toxic substances. Both Kark [8] and Mackey [9] attributed the development of hemochromatosis in their patients to the inability of the body to utilize or excrete the iron introduced in the form of hemoglobin. The latter writer felt that the amount of iron recovered from the patient's liver was directly related to the amount of hemoglobin administered in transfusions. Bomford and Rhoads [5] did not commit themselves regarding the relationship of hemochromatosis to transfusions and stated that 2 of their patients had not received an exceptional number of transfusions.

In our case, the liver contained the excessive amount of 29 Gm. of iron. During the entire illness our patient received 12.8 liters of blood in seventeen transfusions. Only about 6.5 Gm. of iron was introduced into the body by this means. This leaves an excess of 22.5 Gm of iron.

Studies of the excretion of urobilinogen by patients with pseudoaplastic anemia indicate increased hemolysis in many instances.[5] This factor may account for some of the iron present in the organs of our patient.

Although no studies of the metabolism of porphyrin were done in our case, there is evidence that the pigment metabolism in aplastic anemia differs from that in any other type of anemia. The increased excretion of type III coproporphyrin which occurs in some instances of aplastic anemia [32] is also found in lead poisoning [33] and after the administration of arsphenamine [34] and sulfanilamide.[35] On this basis, Dobriner, Rhoads and Hummel [32] suggested that aplastic anemia may result from intoxication. It is interesting to note that Kark's patient,[8] reported as having the first case of aplastic anemia and hemochromatosis, had, in addition to pigmentation of the skin and of the conjunctivas, discoloration of the teeth, one of the classic symptoms of congenital porphyria. So far as we know, discoloration of the teeth associated with hemochromatosis has never been described. Disturbances of the metabolism of porphyrin occur frequently in diseases of the liver [36] and have been noted in patients with hemochromatosis.[37] This fact raises the question whether the porphyrinuria occurring in various intoxications, in aplastic anemia, in hemochromatosis and in diseases of the liver is not due entirely to hepatic dysfunction.

In our case, sulfobromophthalein excretion and cephalin flocculation tests gave negative results. Only the abnormal response to parenterally administered synthetic vitamin K suggested damage to the liver.[38] Barker,[39] using various tests of hepatic function, found evidence of damage to the liver in more than half of his patients with all types of anemia.

That hemochromatosis is due to an inborn error of intracellular iron metabolism is generally recognized.[40] However, some investigators [41] have emphasized the importance of the cirrhosis

31. Whipple, G. H., and Robscheit-Robbins, F. S.: Hemoglobin Production Factors in the Human Liver, J. Exper. Med. **57**:671 (April) 1933; Hemoglobin Production Factors in the Human Liver, ibid. **76**:283 (Sept.) 1942. Balfour, W. M.; Hahn, P. F.; Bale, W. F.; Pommerenke, W. T., and Whipple, G. H.: Radioactive Iron Absorption in Clinical Conditions: Normal, Pregnancy, Anemia, and Hemochromatosis, ibid. **76**:15 (July) 1942.

32. Dobriner, K.; Rhoads, C. P., and Hummel, L. E.: Excretion of Porphyrin in Refractory and Aplastic Anemia, J. Clin. Investigation **17**:125 (March) 1938.

33. Watson, C. J.: Concerning the Naturally Occurring Porphyrins: Urinary Porphyrin in Lead Poisoning as Contrasted with That Excreted Normally and in Other Diseases, J. Clin. Investigation **15**:327 (May) 1936.

34. Hoerburger, W., and Fink, H.: Ueber Porphyrine bei klinischer Porphyrie, Ztschr. f. physiol. Chem. **236**: 136, 1935.

35. Rimington, C., and Hemmings, A. W.: Porphyrinuria Following Sulphanilamide: Sulphanilamide Dermatitis, Lancet **1**:770 (April 2) 1938.

36. (*a*) Nesbitt, S.: Excretion of Coproporphyrin in Hepatic Disease: IV. Isolation and Identification of Urinary Coproporphyrin Isomers, Arch. Int. Med. **71**:483 (April) 1943. (*b*) Dobriner, K.: Urinary Porphyrins in Disease, J. Biol. Chem. **113**:1 (Feb.) 1936.

37. Dobriner.[36b] Dobriner, K.: Porphyrin Excretion in the Feces in Normal and Pathological Conditions, J. Biol. Chem. **120**:115 (Aug.) 1937. Vannotti, A.: Porphyrine und Porphyrinkrankheiten, Berlin, Julius Springer, 1937, p. 145. Lageder, K.: Klinische Porphyrinuntersuchungen mit einer quantitativen spektroskopischen Methode, Arch. f. Verdauungskr. **56**: 237 (Nov.) 1934. Eppinger, H.: Die Leberkrankheiten, Berlin, Julius Springer, 1937, p. 426.

38. Data concerning the test referred to will be presented in another communication, by Dr. Shepard Shapiro.

39. Barker, W. H.: Excretion of Bile Pigment and Hepatic Function in Diseases of the Blood, Arch. Int. Med. **62**:222 (Aug.) 1938.

40. Dry, T. J.: Hemochromatosis: Its Relation to the Metabolism of Iron and Copper, Minnesota Med. **17**:301 (June) 1934. Sheldon.[12] Butt and Wilder.[14]

41. Potter, N. B., and Milne, L. S.: Bronzed Diabetes, Am. J. M. Sc. **143**:46 (Jan.) 1912. Gaskell and others.[21]

of the liver. In contrast to idiopathic hemochromatosis, there is evidence that increased hemolysis is a factor in the evolution of hemochromatosis associated with pseudoplastic anemia. Additional factors, however, must be operative to produce the lesions of hemochromatosis as distinct from those of hemosiderosis.

The cause of aplastic anemia is obscure, but its relationship to exogenous and endogenous toxins [5] is assumed. Such toxic elements, possibly in connection with deficiency factors, may lead to permanent damage to the liver. Thus, patients with pseudoaplastic anemia with prolonged course come to have retention of iron, pigmentation, and cirrhosis of the liver and, as the pancreas becomes involved, diabetes develops.

SUMMARY AND CONCLUSIONS

Although both aplastic anemia and hemochromatosis are comparatively rare diseases, their occurrence together has been recorded in 5 instances, an incidence which, we believe, is altogether too high to be regarded as accidental. In 4 of the 5 cases referred to the changes in the bone marrow were described as pseudoaplastic.

The case which we have reported here is that of a patient with pseudoaplastic anemia whose body at autopsy revealed the lesions that are characteristic of hemochromatosis. Similarities occur between hemosiderosis, which is frequently found in certain anemias, and hemochromatosis, in which anemia, if present, is merely a complicating factor. Hemosiderosis and hemochromatosis are, we believe, separate disease entities.

In an attempt to correlate the changes in pseudoaplastic anemia with those in hemochromatosis we have considered the question of the origin of the iron in both conditions together with the available evidence of hepatic dysfunction.

The iron derived from the destruction of intrinsic and of transfused blood is not used in the formation of hemoglobin but is mechanically deposited in various organs. If the aplastic anemia is of sufficient duration, large quantities of iron accumulate. We believe that view to be sound which holds that aplastic anemia is due to toxins. These toxins, together with other factors, possibly nutritional, may lead to permanent hepatic damage in the form of cirrhosis. The increased amount of iron in the presence of cirrhosis of the liver produces a picture indistinguishable from that of hemochromatosis.

In contrast to idiopathic hemochromatosis, increased hemolysis is active in the production of hemochromatosis when it is associated with pseudoaplastic anemia.

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PERNICIOUS ANEMIA IN CHINESE

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Pernicious anemia has generally been considered a disease of Caucasians. In a recent review [1] we pointed out that its occurrence in Negroes is by no means uncommon and that the recognition of this fact should make for more frequent diagnosis. Textbooks in general, and hematologic texts in particular, stress the great infrequency of pernicious anemia in Chinese. This impression is borne out by a study of the literature. Notwithstanding this fact, we have had occasion to recognize and study 3 cases of typical pernicious anemia in native-born Chinese who had lived for many years in the Chinese community of Chicago.

REVIEW OF THE LITERATURE

The cases reviewed by Struther [2] were incompletely worked up and did not fulfil the diagnostic criteria of pernicious anemia. In response to his questionnaire, Berglund wrote that no Chinese patient with this disease had been seen at the Peking Hospital. Fu and Sturton [3] reported a case in Hangchow, but the records concerning the gastric juice and the nervous system were incomplete. Morris [4] found 6 cases in the hospital records of Central and North China, but these were not documented, and in his own experience there were no proved cases. Williams' [5] report of a case was also incomplete, and his patient improved after four weeks in the hospital without liver therapy. The patient's further course was not followed.

De Langen and Lichtenstein [6] stated that they had never seen pernicious anemia among the poor Chinese in Batavia but that an occasional case has been observed among the wealthier patients.

According to Snapper [7], macrocytic nutritional anemia occurs frequently in the Orient, but true pernicious anemia is rare. The 6 cases reported by him from the Peiping Union Medical College Hospital had features which were atypical for pernicious anemia. The patients responded to small doses of liver and remained free from recurrences for years without liver therapy or with only small doses of liver. They showed rapid improvement of extensive neurologic changes with liver therapy or sometimes with adequate diet alone. There was a return of free hydrochloric acid with the disappearance of the anemia, and the expected anisocytosis and poikilocytosis were absent from the blood. Snapper expressed the opinion that "it seems hardly feasible to conclude that this group of patients really suffered from genuine pernicious anemia, although one may still readily agree that their anemia was closely related to pernicious anemia."

Yang and Keefer [8] have reported the only 2 cases of pernicious anemia in Chinese observed previously on this continent. They were cases of Minot's and apparently were typical.

REPORT OF CASES

CASE 1.—H. T. Y., a 55 year old man, a native Chinese, was admitted to the hospital Jan. 29, 1935, because of vomiting of one week's duration, loss of weight, anorexia and weakness of six months' duration and tingling of the fingers and toes and soreness of the tongue of one year's duration. Physical examination revealed nothing abnormal except extreme pallor and atrophy of the papillae of the tongue. Examinations of the sputum, stools, urine and spinal fluid were noncontributory. Roentgen ray examination of the gastrointestinal tract revealed nothing abnormal. No free acid and 10 degrees of total acid were found in tests of the contents of the stomach after an Ewald meal. Hematologic values were typical of pernicious anemia in relapse (chart 1). Response to liver therapy was satisfactory, and he was discharged from the hospital on March 16. He received liver therapy as an outpatient until June 20, when he disappeared from observation until Nov. 14, 1936. At that time he again presented himself in a state of relapse. Response to therapy was satisfactory, and

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From the Hematology Laboratory and the Hektoen Institute for Medical Research of the Cook County Hospital.

1. Schwartz, S. O., and Gore, M.: Pernicious Anemia in Negroes, Arch. Int. Med. **72**:782 (Dec.) 1943.

2. Struther, G.: Discussions of Anemias in China, Chinese M. J. **43**:818, 1929.

3. Fu, W. T., and Sturton, S. D.: A Severe Case of Pernicious Anemia, Chinese M. J. **40**:1016, 1926.

4. Morris, H. H.: Anemia in China, Chinese M. J. **43**:768, 1929.

5. Williams, T. H.: Pernicious Anemia in Szechwan, Chinese M. J. **46**:673, 1932.

6. De Langen, C. D., and Lichtenstein, A.: Textbook of Tropical Medicine, Batavia, Java, G. Kolff & Co., 1936, p. 487.

7. Snapper, I.: Chinese Lessons to Western Medicine, New York, Interscience Publishers, Inc., 1941, p. 264.

8. Yang, C. S., and Keefer, C. S.: Pernicious Anemia in Chinese Patients, Nat. M. J. China **17**:218, 1931.

he continued well until January 1940 with somewhat intermittent treatment. He was last seen on Sept. 3, 1941. He was in good health and had had no liver except small amounts eaten occasionally. The achylia was still in evidence on the second admission.

CASE 2.—W. L. Y., a 60 year old man, a native Chinese, was admitted to the hospital June 6, 1940, complaining of soreness of the tongue, difficulty in swallowing, loss of weight, numbness of the fingers and vertigo. On examination he was found to have a smooth, red tongue, jaundice of the scleras and hyperactive knee jerks. Laboratory findings of interest were a histamine-fast achlorhydria and an icterus index of 15. Hematologic values were typical of pernicious anemia in relapse (chart 2). Response to liver therapy was satisfactory, and the patient has been maintained in good health with average amounts of liver extract to the time of writing. The achlorhydria—even after injections of histamine—was still present on July 28, 1944.

CASE 3.—L. B., a 73 year old man, a native Chinese, was first admitted to the hospital on March 1, 1943. Because of his inability to speak English and his extreme illness, no history was elicitable. The extreme pallor, vitiligo of the skin and jaundice of the scleras were the most prominent observations made in the examination. There was noted, in addition, a greatly distended bladder which extended to within a few centimeters of the umbilicus. Laboratory findings of interest were the decidedly elevated icteric index (37), the histamine-fast achlorhydria and the hypercellular marrow with typical megaloblastic maturation of the cells. Hematologic values were typical of pernicious anemia in relapse (chart 3) and improved rapidly with liver therapy alone. On March 30, he left the hospital, but,

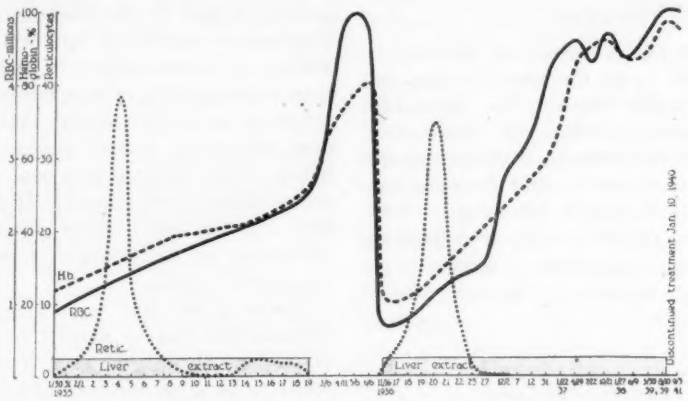

Chart 1 (case 1).—Characteristic reticulocyte response and rise in red cells and hemoglobin following administration of liver, with relapse after the discontinuance of therapy and a second response almost identical with the first.

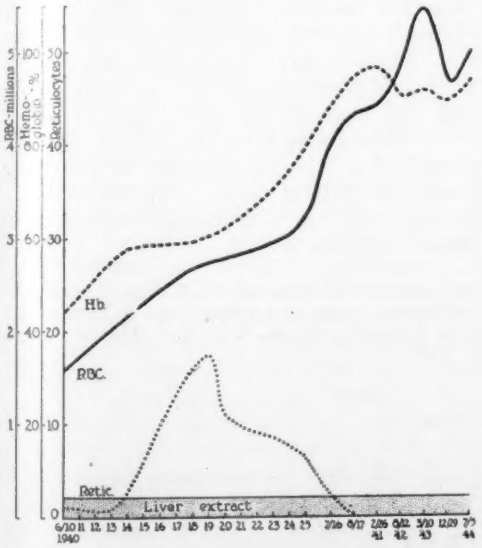

Chart 2 (case 2).—Typical red cell, hemoglobin and reticulocyte response following liver therapy.

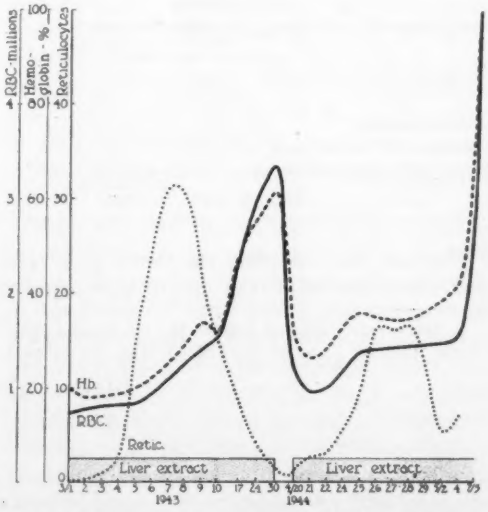

Chart 3 (case 3).—Response resembling that in case 1. It is to be noted that therapy was discontinued before complete remission occurred after the first course of treatment, and yet more than a year elapsed before the second relapse.

failing to return for injections of liver extract, he reentered in relapse on April 20, 1944. The findings at this time were essentially as previously noted, except that the icteric index now was only 21. He again responded uneventfully and was discharged on May 4. Since then he has been cared for in the outpatient clinic and has been well maintained. The jaundice has disappeared. Symptoms referable to the bladder are absent. The achlorhydria has persisted (rechecked with histamine July 28, 1944).

COMMENT

Using for criteria of pernicious anemia the macrocytic anemia (with the accompanying anisocytosis and poikilocytosis), the permanent achlorhydria, megaloblastic cell maturation, signs of increased pigmentary metabolism, neurologic changes and remission after the exhibition of liver therapy and relapse following its withdrawal,[9] one notes that all 3 cases are typical instances of Addison's (pernicious) anemia of the type seen in the Caucasian. These criteria are outlined in the table.

Characteristic Clinical and Laboratory Observations in the Three Reported Cases

	Case 1	Case 2	Case 3
Macrocytic anemia	+	+	+
Permanent achlorhydria	+ (Only once examined)	+	+
Megaloblastic cell maturation	No studies of the marrow	No studies of the marrow	+
Evidences of increased pigmentary metabolism	No pigmentary studies	+	+
Neurologic changes	+	+	+
Remission after liver therapy	+	+	+
Relapse after discontinuance of liver therapy	+	Has not discontinued therapy	+

The fact that we could encounter, in a relatively short period of time and in an institution in which orientals are relatively rare, 3 Chinese with this disease which is said to occur with extreme rarity in members of this race in their native environs raises some interesting questions. Is pernicious anemia really rare in the Chinese of China, or is it their relatively infrequent contact with western physicians which merely makes it appear so? Has the teaching that pernicious anemia is rare in the Chinese influenced some clinicians to prefer to interpret the macrocytic anemia as one secondary to malnutrition rather than to accept it as true pernicious anemia? We are in no position to answer these questions. Or does pernicious anemia appear only when the native is transplanted to a new (and apparently unfavorable) environment? If this is the case, then one may ask whether it is the physical environment or the changed dietary habits that induce the anemia.

There is certainly no evidence that physical environment plays a signal role. Dietary habits could be a factor, but such a conclusion would seem to be a paradox in view of the generally accepted belief that the American diet is nutritionally superior. Two other possibilities suggest themselves. The first is that environmental, infective, nutritional and perhaps physical circumstances leading to gastritis may in time sufficiently interfere with production of the intrinsic factor to give rise to pernicious anemia. The second possibility is that the increased fat in the American diet may be a cause.[10]

With the increasing interest in China and the probability of more opportunity to study the Chinese, it will be of considerable interest to see whether more cases of pernicious anemia in Chinese will come to light.

9. Schwartz, S. O., and Legere, H.: Relapses in Pernicious Anemia, J. A. M. A. **124**:637 (March 4) 1944.

10. Johnson, V.; Freeman, L. W., and Longini, J.: Erythrocyte Damage by Lipemic Serum in Normal Man and in Pernicious Anemia, J. A. M. A. **124**:1250 (April 29) 1944.

LARGE DOSES OF ASCORBIC ACID IN TREATMENT OF VITAMIN C DEFICIENCIES

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Patients entering a hospital with a variety of complaints are often found to have low levels of ascorbic acid in the plasma if determinations of this factor are made. In some cases in which diagnosis or treatment may be facilitated by the restoration of vitamin C in the tissues, rapid saturation is desired. To accomplish this efficiently, it is necessary to determine the maximum dose that will not cause increased urinary excretion of ascorbic acid. Obviously the total dose required for saturation depends on the state of deficiency of the body tissues, and one can judge that amount only by some indirect index of the status of the tissues. It has been argued that the plasma level of ascorbic acid is a poor index, and attempts have been made to find more reliable criteria for the state of vitamin C nutrition. Studies of excretion, although extensive, have not established a definite normal standard. Experiments concerning saturation have furnished valuable data but still have not proved whether good vitamin C nutrition entails a saturation level or something less. The level of ascorbic acid in the whole blood has been suggested [1] as being more truly representative of the general body status of vitamin C nutrition than the level in the plasma, since the cell content of this vitamin does not fluctuate as rapidly as does the plasma content. Further reasoning along this line has led some investigators [1b] to prefer the use of the white cell and platelet layer of the blood as an index of vitamin deficiency in the tissues. It was noted that the white blood cells retained appreciable amounts of vitamin C after the plasma content was reduced to very low levels, and therefore it was argued that plasma values did not reflect tissue need. However, it must be remembered that vitamin C is not evenly distributed throughout the body tissues. In the ovaries and in the adrenal and the pituitary glands, for example, the concentration is much higher than in some of the other glands or in muscle. Until the mechanism of function is known, the separate needs of the different tissues for this vitamin cannot be evaluated. The plasma obviously is the vehicle of transport and might not reflect deficiency in the tissues if extensive storage of vitamin C occurs. There is little evidence that much is stored, in which case persistently low plasma levels of vitamin C must mean deprivation somewhere along the route. In any event, when a vitamin C deficiency is suggested clinically and the dietary history is poor, a low plasma value is corroborative evidence. Our observations in connection with this and other studies have led to the belief that persons, sick or well, who regularly include adequate amounts of vitamin C–containing food in the diet and who have no evidence of oral disease seldom have fasting plasma values lower than 0.8 mg. per hundred cubic centimeters. The amount of administered ascorbic acid retained by the body may indicate the state of depletion in the tissues, but in excretion tests collection of specimens is more time consuming and not always convenient, besides which the assay itself (as in the case of determinations of whole blood or of white cell content) is not as simple as determination of plasma content of vitamin C. Therefore, in addition to observations on the efficiency of large doses of ascorbic acid in treatment of vitamin C deficiency, we have presented some data on plasma levels at the various stages of depletion up to saturation with corresponding excretions of the various doses of ascorbic acid in an attempt to further the knowledge that would justify the clinical use of this convenient test.

MATERIALS AND METHODS

The data here reported for 26 hospital patients, unselected as to disease except for clinical and laboratory indications of vitamin C deficiency, include determina-

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1. (*a*) Heinemann, M.: The Distribution of Ascorbic Acid Between Cells and Serum in Relation to Its Urinary Excretion, J. Clin. Investigation **17**:751 (Nov.) 1938. (*b*) Butler, A. M., and Cushman, M.: Distribution of Ascorbic Acid in the Blood and Its Significance, ibid. **19**:459 (May) 1940.

tions of levels in plasma, whole blood and urine, before and after large oral doses of ascorbic acid or intravenous injections of sodium ascorbate.

The method used for determinations of vitamin C in whole blood and urine was that of Roe and Kuether [2]; for determinations in plasma, the Mindlin-Butler macromethod.[3] Determinations of levels in whole blood and in plasma were made within a three hour period after the blood samples were obtained. Determinations of urinary levels were made on fresh material for most of the fractional specimens, and twenty-four hour specimens were examined as soon as the collection period was ended. All urine was kept in brown bottles placed in a container with ice; and when the collection period was prolonged, glacial acetic acid was added as a preservative. Duplicate readings on fresh and on preserved aliquots of the same specimen showed no loss of ascorbic acid by this method of preservation over a twenty-four hour period.

The clinical selection of patients for this study was based on dietary history suggesting gross deficiency of raw fruit and vegetable foods or on visible evidence of edema, redness, retraction or inflammation of the gums or of frank pyorrhea alveolaris.

TABLE 1.—*Efficiency of Large Doses of Ascorbic Acid*

Number of Doses			Excretion of Ascorbic Acid		
			Mg./Hour		Average,
Intravenous	Oral	Dose, Mg.	Average	Range	Mg./24 Hours
6	9	100	0.33	0.2 -0.5	7.9
6	5	200	0.82	0.04-2.3	13.6
	10	300	0.34	0.04-0.7	8.3
	19	400	0.35	0.06-1.2	8.3
4	10	500	0.83	0.2 -3.0	19.9
	3	1 Gm.	0.50	0.3 -0.6	12.0
Basic excretion of 11 subjects			0.24	0.08-0.44	5.7

RESULTS AND COMMENT

In table 1 a condensation of part of the data shows that single doses as high as 1 Gm. of ascorbic acid were given without significant urinary loss. A variation in the number of hours of collection of urine with different doses is the result of an attempt at detail by fractionating all specimens of urine when the daily dose was divided, so that each specimen included the immediate excretion after one dose of ascorbic acid. Therefore, as shown in table 1, the average excretion for a twenty-four hour period was in many instances obtained from figures on twenty-four hour excretion calculated on the basis of actual excretion each hour for fractional periods varying from three to fifteen hours. In 11 subjects the twenty-four hour excretion of ascorbic acid prior to supplementation with doses of the vitamin ranged from 2 to 11 mg. Because plasma levels for the group were within the same range, we did not delay treatment in every case to determine pretreatment excretion. The plasma level (and occasionally the whole blood level) was determined in all but 1 instance. These basic levels were between 0 and 0.39 mg. per hundred cubic centimeters, except for subject 1 in table 2.

Averages for 200 and 500 mg. doses are out of line because of the inclusion of figures on intravenous doses. This method of administration tended to produce higher excretions, as already indicated by van Eekelen and Heinemann.[4] Inspection of table 2 shows that in every instance intravenous therapy resulted in a larger excretion than did an oral dose of the same amount in the same or in different patients, when plasma levels were similar, as, for example, in subjects 22 and 23. However, the magnitude of this difference in excretion between oral and intravenous administration is not such as to constitute a large fractional loss of the dose administered while the patient is still seriously deficient in vitamin C.

Daily doses of ascorbic acid and the results of administration of various amounts are presented in table 2. The table gives a more accurate picture of the correlation between plasma and excretion and of the efficiency of rapid saturation. All plasma readings were made on fasting blood samples, that is, from blood drawn in the morning before breakfast, at least twelve hours after ingestion of food or ascorbic acid. During the period in which ascorbic acid was administered, the pairing of values for excretion and for plasma was based on the blood sample which was obtained at the end of the twenty-four hour period of collection of urine. Complete data on all patients could not be obtained for several reasons. However, on a number of subjects we were able to obtain fairly complete figures concerning daily plasma level and urinary excretion; hence it was possible to place the day on which excretion over 40 mg. first occurred and the first day of excretion of 50 per cent of the ingested dose. The use of 40 mg. every twenty-four hours as a measure of normal excretion is arbitrary. In our present series, from examination of the data on fractionated specimens, we

2. Roe, J. H., and Kuether, C. A.: The Determinations of Ascorbic Acid in Whole Blood and Urine Through the 2,4-Dinitrophenylhydrazine Derivative of Dehydroascorbic Acid, J. Biol. Chem. **147**:399 (Feb.) 1943.

3. Mindlin, R. L., and Butler, A. M.: The Determination of Ascorbic Acid in Plasma: A Macromethod and a Micromethod, J. Biol. Chem. **122**:673 (Feb.) 1938.

4. van Eekelen, M., and Heinemann, M.: Critical Remarks on the Determination of Urinary Ascorbic Acid, J. Clin. Investigation **17**:293 (May) 1938.

noted that to reach an excretion level above 40 mg. every twenty-four hours usually 75 per cent or more of the total saturation dose was needed. Published data on normal excretion or usual excretion with a normal diet give figures ranging from 13 to 35 mg. every twenty-four hours.[5] Until recently the methods for assaying urinary content of vitamin C measured the reduced ascorbic acid only, while our values for excreted vitamin C represent the total ascorbic acid in

TABLE 2.—*Results of Daily Doses of Ascorbic Acid in Twenty-Seven Patients*

	Basic Levels		Supplemented Levels						
Subject	Plasma, Mg. per 100 Cc.	Excretion 24 Hours, Mg.	Daily Dose, Mg.	Administration	Plasma, Mg. per 100 Cc.*	Excretion 24 Hours, Mg.	Sex	Age	Diagnosis
1	0.62	7	100	Oral	0.59	6	F	31	Psychoneurosis
			100	Oral	0.52	7			
2	0	..	200	Oral	0.03	1	M	72	Parkinson's disease; arteriosclerosis; duodenal diverticulum
			200 6 days	Oral	1.53	70			
3	0	2	300	I. V.*	0	5	M	63	Carcinomatosis; arteriosclerotic kidneys
			300	I. V.	0	8			
4	0.20	11	300	Oral	0.47	13	M	45	Hyperparathyroidism; generalized vitamin deficiencies
			300	Oral	0.92	32			
			300	Oral	1.12	234			
5	0.10	7	300	Oral	....	9	F	15	Bronchial asthma; ovarian hypofunction
			300 4 days	Oral	1.37	29			
			300 6 days	Oral	1.40	214			
6	0.10	..	500	Oral	0.30	7	M	59	Hypertensive heart disease with reduced renal function
7	0	2	600	I. V.	0	20			
			600	I. V.	0	29			
8	0.05	11	600	Oral	0.19	11	M	58	Hypertensive cardiorenal disease
			600	Oral	0.46	68			
			600	Oral	0.79	112			
			600	Oral	1.28	207			
9	0.24	..	600	Oral	0.83	11	M	51	Gastric carcinoma
9	0.25	..	600	Oral	0.87	39	M	62	Gastric carcinoma
10	0	..	600	Oral	0.65	11	M	72	Gastric ulcer
11	0.04	6	600	Oral	0.74	10	F	21	Scurvy with arthritis
			600 4 days	Oral	0.65	384			
12	0.13	4	(400)	Oral	....	(4)	M	47	Spastic bowel; migraine; pyorrhea
			800	Oral	....	4			
			800	Oral	1.67	186			
13	0.39	..	800	Oral	0.90	13	M	71	Hypertrophic arthritis; arteriosclerosis
14	0.36	..	800	Oral	1.11	351	M	72	Rheumatoid arthritis
15	0.15	..	800	Oral	0.71	10	M	43	Malnutrition; psychoneurosis
16	0	4	800 2 days	Oral	0.14	6	M	41	Gastric ulcer
			800	Oral	0.91	4			
17	0.13	..	800	Oral	0.88	4	M	29	Neurocirculatory asthenia
18	0.05	3	800 2 days	Oral	0.29	2	M	20	Ulcerative colitis
			800	Oral	0.52	4			
19	0	..	1 Gm.	I. V.	0	15	M	36	Myelogenous leukemia
			1 Gm.	Oral	0	8			
			1 Gm.	Oral	0	14			
			1 Gm.	Oral	0.08	6			
20	0	..	1.5 Gm.	I. V.	0.62	134	M	56	Ulcerative colitis; slightly reduced kidney function
21	0	..	1.5 Gm.	I. V.	0	134	M	46	Hodgkin's sarcoma; suggested renal damage
22	0.27	..	1.5 Gm.	I. V.	1.50	582	M	60	Nonmalignant cyst of tongue
23	0.24	..	1.5 Gm.	Oral	1.49	82	M	45	Recurrent duodenal ulcer
24	0.10	..	1.5 Gm.	Oral	1.35	118	M	57	Arteriosclerotic heart failure; duodenal ulcer; pyorrhea
19	0	..	1.5 Gm.	I. V.	0	35			
25	....	7		Data incomplete			M	45	Anxiety state with vomiting
26	0	4		Data incomplete			M	54	Duodenal ulcer; extrarenal uremia due to alkali therapy
27	0.14	..		Data incomplete			M	62	Chronic lymphogenous leukemia; renal damage

* I. V. indicates intravenous injections of sodium ascorbate.

5. (*a*) Hawley, E. E.; Stephens, D. J., and Anderson, G.: The Excretion of Vitamin C in Normal Individuals Following a Comparable Quantitative Administration in the Form of Orange Juice, Cevitamic Acid by Mouth and Cevitamic Acid Intravenously, J. Nutrition **11**:135 (Feb.) 1936. (*b*) Finkle, P.: Vitamin C Saturation Levels in the Body in Normal Subjects and in Various Pathological Conditions, J. Clin. Investigation **16**:587 (July) 1937. (*c*) Ralli, E. P.; Friedman, G. J., and Sherry, S.: Vitamin C Requirement in Man: Estimated After Prolonged Studies of the Plasma Concentration and Daily Excretion of Vitamin C in Three Adults on Controlled Diets, ibid. **18**:705 (Nov.) 1939. (*d*) Brown, A. P.; Fincke, M. L.; Richardson, J. E.; Todhunter, E. N., and Woods, E.: Ascorbic Acid Nutrition of Some College Students, J. Nutrition **25**:411 (May) 1943.

the urine, that is, the reduced plus the dehydroascorbic acid. Berryman and others [6] found that dehydroascorbic acid averaged 18 per cent of the total amount excreted. It is generally understood that saturation is indicated by excretion of 50 per cent of the administered dose.

For 20 subjects (table 3), we have sufficient data to obtain information regarding the amount

TABLE 3.—*The Renal Threshold for Ascorbic Acid*

	Plasma, Mg. per 100 Cc.				Cumulative Dosage of Ascorbic Acid, Gm.	
Subject	Basic	After Treatment But Before Spill	On 1st Day of Excretion Over 40 Mg.	Day of Excretion of 50% of Dose	On 1st Day of Excretion 40 Mg.	Day of Excretion of 50% of Dose
8	0.24	0.83	1.91	1.91	1.5	1.5
12	0.13	....	1.67	1.74	2.0	2.8
13	0.39	0.90	1.43	1.43	2.0	2.0
24	0.10	....	1.35	....	1.5	...
14	0.36	....	1.11	1.12	0.8	2.0
25	0.02	....	0.26	....	0.5	...
23	0.24	....	1.49	....	1.5	2.0
1	0.62	0.52	1.50	....	0.5	...
7	0.05	0.19	0.46	1.28	0.6	2.4
2	0	0.96	1.53	1.42	1.2	1.4
10	0	0.65	1.51	1.51	1.5	1.5
22	0.27		1.50		1.5	
4	0.20	0.92	....	1.12	0.9	1.5
11	0.04	0.74	0.67	0.67	1.8	1.8
5	0.10	1.37	1.50	1.40	1.5	1.8
16	0	0.91	Not reached	....	Not reached on 2.4	...
9	0.25	0.87	1.34	....	1.5	...
17	0.13	0.88	1.40	1.40	2.0	2.0
6	0.10	0.30	0.63	0.60	1.5	2.5
20	0	....	0.62	....	1.5	...

of ascorbic acid needed to bring the excretion of vitamin C to normal and saturation levels. It will be noted that in many cases the subject's plasma level is fairly high before the excretion has reached 40 mg. Subjects who reached the saturation point within twenty-four hours had, of course, no reading between the basic and saturation levels. In 15 subjects the plasma level was over 1.0 mg. per hundred cubic centimeters at the time the excretion reached 40 mg. Of the 5 exceptions, it may be noted in table 2, 4 suffered disturbed or damaged renal function. The condition of the fifth was diagnosed as scurvy with arthritis. It is not known that scurvy affects the renal tubules so as to lower the ascorbic acid threshold. Russel and Calloway,[7] in a report of experiments on guinea pigs, described changes in the cytoplasm of the cells of the convoluted proximal tubules in the scorbutic animals and conclude that vitamin C deficiency produces a pathologic change in the cells of the kidney. Since scurvy does cause deterioration of the supporting tissues throughout the body and apparently alters the structure of the capillary wall very early, it is possible that the effect on the renal tubules may be to increase permeability to ascorbic acid.

Aside from the (apparently) pathologic renal threshold described in 5 of our cases, the data in table 3 suggest that the threshold for ascorbic acid may vary between 1.12 and 1.91 mg. per hundred cubic centimeters in 10 patients. In 5 additional patients, who had not really reached the saturation point, it is evident that the threshold is not lower than 1.34.

TABLE 4.—*Effects of Administration of Ascorbic Acid on Plasma and on Whole Blood*

Subject	Day	Plasma, Mg. per 100 Cc.	Whole Blood, Mg. per 100 Cc.	Cumulative Dose, Gm
12	Basic	0.13	0.20	...
	3	1.67	1.47	2.0
	4	1.74	1.66	2.8
19	B	0.00	....	...
	1	0.00	....	1.5
	2	0.00	0.76	2.5
	3	....	....	3.5
	4	....	....	4.5
	5	0.08	0.51	5.5
	6	0.00	0.39	6.5
25	B	0.02	0.35	...
	1	0.26	0.58	0.5
	2	0.79	0.86	1.0
3	B	0.00	0.06	...
	1	0.00	0.09	0.3(I.V.)
	2	0.00	0.15	0.6
	3	....	0.23	1.2
	4	....	0.38	1.8
	5	0.34	0.72	2.4
	6	0.65	0.90	3.4
	7	0.36	0.74	3.4
2	B	0.00	....	...
	6	1.53	1.68	1.2
	7	1.42	1.77	1.4
21	B	0.00	0.12	...
	1	0.00	0.46	1.5
	2	0.37	0.51	2.5
M. D.	B	0.69	....	...
	1	0.58	0.69	0.1
M. B.	B	1.10	....	...
	4	1.40	1.48	0.4

Some data on comparisons of whole blood and plasma are given in table 4. Readings were made on the same blood sample in each case. Most of the observations were made on the subjects of this series in connection with excretion studies, but a few additional ones are from normal subjects obtained at various times throughout the past year.

6. Berryman, G. H.; French, C. E.; Harper, H. A., and Pollack, H.: Response to the Intravenous Injection of Ascorbic Acid as Indicated by the Urinary Excretion of the Total and Reduced Forms, J. Nutrition **27**:309 (April) 1944.

7. Russel, W. O., and Calloway, C. P.: Pathologic Changes in the Liver and Kidneys of Guinea Pigs Deficient in Vitamin C, Arch. Path. **35**:546 (April) 1943.

It still appears, from what we have observed, that whole blood is no more valuable than plasma in estimating the patient's need for vitamin C therapy. In the low ranges, which are of concern to the diagnostician, the whole blood level of ascorbic acid was higher than its plasma level, but the greatest difference found was 0.12 mg. per hundred cubic centimeters, except only in the case of subject 25, who had been receiving a high alkali intake, from which evident disturbance of renal function had occurred. It is known that vitamin C is destroyed by alkali, and the fact that at the time of the first blood sample alkali therapy had not been stopped suggests the possibility of destruction of vitamin C in the plasma out of proportion to destruction of that in the cells. Furthermore, it will be noted that on the third day after cessation of therapy (table 4) the divergence of 0.33 was decreased to 0.07 mg. per hundred cubic centimeters, a figure which is in line with the others.

TABLE 5.—*Ascorbic Acid Levels in Plasma Compared with Those in Whole Blood*

Plasma Levels 0.0 to 0.16 Mg./100 Cc.			Plasma Levels Over 1.0 Mg./100 Cc.			Plasma Levels Over 1.0 Mg./100 Cc.		
Plasma	Whole Blood	Difference	Plasma	Whole Blood	Difference	Plasma	Whole Blood	Difference
0.00	0.06	0.06	1.05	1.17	0.12	1.42	1.77	0.35
0.00	0.08	0.08	1.12	1.20	0.08	1.53	1.68	0.15
0.00	0.09	0.09	1.30	1.36	0.06	1.67	1.47	—0.20
0.06	0.18	0.12	1.40	1.48	0.06	1.74	1.66	—0.08
0.08	0.13	0.05	Range 0.06 to 0.12			1.77	1.98	0.21
0.08	0.13	0.05				Range 0.08 to 0.35		
0.13	0.20	0.07						
0.16	0.23	0.07						
Range 0.05 to 0.12								

In making the comparison of whole blood level and plasma level for values above 1.0 mg. we included some normal persons. We have seen no normal persons with values in the low ranges just discussed. The remainder of the comparisons are made on samples from patients after treatment with ascorbic acid. In four pairs the greatest divergence was 0.12, the same as for the low group. Five pairs in which all values were above 1.40 mg. showed a divergence from 0.08 to 0.35, and in two of these samples the plasma value was higher than that of the whole blood. In none of the others was the plasma higher than the whole blood. Further study in this field is contemplated to allow us to investigate the relationship between whole blood and plasma, especially at threshold levels. It may be that blood cells will carry higher concentrations of vitamin C than the plasma until a point —perhaps 1.4 mg. or over—is reached, after which an equilibrium seems to be established. It becomes increasingly difficult to increase the cell concentration of ascorbic acid by greater forced intake of vitamin C. Faulkner and Taylor [8] have previously reached the conclusion that ascorbic acid is a threshold substance with a critical level of excretion in the vicinity of 1.40 mg. per hundred cubic centimeters of plasma, and Heinemann [9] stated that rapid excretion by the kidneys takes place when the serum level of vitamin C passes 1.40 mg. While supplements were being administered to deficient subjects, it may be noted that (table 4) the relationship between whole blood and plasma was considerably altered.

Included in table 4 is 1 case of myelogenous leukemia (no. 19) in which the plasma level remained zero or nearly so throughout six days while 6.5 Gm. of ascorbic acid was administered. The whole blood level was not obtained until after 2.5 Gm. had been received intravenously, at which time it reached the highest value recorded. Although the treatment was continued, the level dropped appreciably. Loss by excretion was not a factor, as the figures show. High voltage roentgen ray therapy to the spleen was applied daily, and toward the end of the period the drop in the white cell count was great. This may account for the decrease in whole blood content of vitamin C, since the white cells contain a greater concentration of vitamin C than any of the other constituents of the blood. However, the problem posed by the disappearance of these enormous doses of ascorbic acid can be answered only by the assumption that the administered vitamin is destroyed. In cases such as these, plasma studies are obviously inadequate, and the problem must be attacked from several angles. Butler and Cushman have published some data on the subject.[1b] It is felt that study of the white cell and platelet layer of the blood will furnish more information than studies of the whole blood. Until an adequate number of cases are studied and the effects of roentgen ray therapy carefully scrutinized, it is useless to theorize.

FACTORS INFLUENCING INDIVIDUAL REQUIREMENTS OF VITAMIN C

The amount of vitamin C needed to prevent signs of deficiency or to restore deficient levels

8. Faulkner, J. M., and Taylor, F. H. L.: Observations on the Renal Threshold for Ascorbic Acid in Men, J. Clin. Investigation **17**:69 (Jan.) 1938.

9. Heinemann, M.: Distribution of Ascorbic Acid Between Cells and Serum of Human Blood, J. Clin. Investigation **20**:39 (Jan.) 1941.

to normal levels appears to be little affected by a variation in age in men between the ages of 20 and 75. There seems to be some evidence of effects of sex variation. Our observations on women are limited but tend to corroborate Mickelsen's[10] data which indicate fluctuations in plasma content of ascorbic acid corresponding to certain phases in the menstrual cycle. This suggestion of a relation between vitamin C and estrogens is not a new idea. Among others, Selkurt and associates,[11] on the basis of experimentation with animals (dogs), made the statement that "estradiol benzoate increases the clearance of ascorbic acid by reducing tubular reabsorption so that the rate of excretion is increased while the plasma level tends to be reduced." They noted that in the normal dog tubular reabsorption of ascorbic acid is incomplete at plasma levels considerably below those required to effect complete saturation of the tubules; consequently ascorbic acid is excreted in the urine at all plasma levels. In the course of treatment with estradiol benzoate, it was necessary to increase the load level of ascorbic acid considerably in order to produce a maximal reabsorption equivalent to the normal.

As it was previously pointed out, certain diseases apparently affect the efficiency of the body in handling administered ascorbic acid. Renal damage or disturbance in every instance impaired the efficiency, especially with the larger doses. While the effect in our cases seems to be a lowered renal threshold for ascorbic acid, the opposite effect has been observed in other kinds of renal damage.[12] An altered response to therapy was noted in conditions of leukemia, Hodgkin's sarcoma and scurvy.

10. Mickelsen, O.; Dippel, A. L., and Todd, R. L.: Plasma Levels in Women During the Menstrual Cycle, J. Clin. Endocrinol. **3**:600 (Nov.) 1943.

11. Selkurt, E. E.; Talbot, L. J., and Houck, C. R.: The Effect of the Administration of Estrogen on the Mechanism of Ascorbic Acid Excretion in the Dog, Am. J. Physiol. **140**:260 (Nov.) 1943.

12. Sendroy, J., and Miller, B. F.: Renal Function as a Factor in the Urinary Excretion of Ascorbic Acid, J. Clin. Investigation **18**:135 (Jan.) 1939.

SUMMARY AND CONCLUSIONS

The effects of large doses of synthetic ascorbic acid on urinary excretion, plasma and whole blood were studied in patients hospitalized for other ailments but judged to be also deficient in vitamin C on the basis of history, clinical signs and low plasma content of ascorbic acid. The results of this study showed that:

1. The efficiency of single doses of ascorbic acid of 100 to 500 mg. was excellent if the plasma level of ascorbic acid was low.

2. Some patients received as much as 1.5 Gm. of ascorbic acid in one day without significant urinary loss, while the plasma content of vitamin C was increased to high normal levels.

3. The total amount of ascorbic acid supplement required to produce a twenty-four hour excretion of 40 mg. or over varied from 0.5 to 2.0 Gm. and the amount required for saturation, from 1.5 to 2.8 Gm.

4. Intravenous administration of ascorbic acid resulted in slightly greater excretion in a few cases.

5. A wide individual variation in the renal threshold for ascorbic acid is strongly indicated, the probable plasma level for this series being between 1.1 and 1.9 mg. per hundred cubic centimeters.

6. It was not demonstrated that a determination of the whole blood level is superior to that of the plasma level in diagnosing vitamin C deficiency. Patients with low plasma values generally excreted very small amounts of ascorbic acid until dosage had raised the plasma levels above 1.0 mg.

7. Disease appears to be one factor that may influence the response to ascorbic acid treatment. Patients having renal involvement or blood dyscrasias responded atypically.

8. Age did not appear to affect the results significantly.

9. Variations that may be attributed to sex differences occurred in the results of ascorbic acid treatment in these patients.

PRIMARY SYSTEMIC AMYLOIDOSIS OF THE ALIMENTARY TRACT

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Primary systemic amyloidosis is a rare disease. It occurs in the absence of predisposing diseases and is characterized by deposition of amyloid chiefly in the tongue, the alimentary tract and the heart. Koletsky and Stecher [1] recently reviewed 24 cases of this disease reported in the American and foreign literature and added 2 cases of their own. Two additional cases have since been reported.[2]

The following case involved an example of this disease with primary involvement of the alimentary tract; it presents several unusual features.

REPORT OF A CASE

M. T., a 66 year old Negress, was admitted to the medical service of the Grady Hospital in July 1943, with the chief complaint of massive hematemesis three hours before admission.

History.—The patient had been seen frequently in the outpatient clinic since 1927, when she came to the hospital because of constipation and poor appetite. At that time she appeared underweight. Her blood pressure was 160 systolic and 114 diastolic. Her symptoms failed to respond to therapy. She first noted a sensation of "fulness" in the epigastrium in 1931, and in 1940 she had frequent attacks of epigastric pain, which were relieved by food. Her symptoms were progressive. A series of gastrointestinal examinations in 1933 showed no pathologic changes, and a study of the gallbladder in 1941 gave results which were interpreted as normal.

For several months prior to her entry into the hospital she had some exertional dyspnea, slight orthopnea and intermittent edema of the ankles. She had occasional dysuria and nocturia, but numerous urinalyses revealed albuminuria of only 1 to 2 plus. Numerous serologic tests for syphilis gave negative results.

One week prior to her entry persistent pain in the lower part of the abdomen developed. She had frequent foul-smelling light yellow stools associated with abdominal cramping. She became progressively weaker. Three hours before her admission severe "drawing" epigastric pain, which radiated to the back, developed, and she vomited about a pint of "coffee-ground" material with flecks of fresh blood.

Physical Examination.—The patient was a weak, emaciated Negress. Her temperature was 99.6 F., her pulse rate 112, her respiratory rate 14 and her blood pressure 200 systolic and 110 diastolic. An indefinite, soft, tender mass was palpated in the midepigastrium. There was no muscular spasm, and peristalsis was present. The apex impulse of the heart was located 11 cm. to the left in the fifth intercostal space. The rhythm was regular, except for occasional premature contractions. There was slight pitting edema of the legs. The lungs were clear. The skin over the forearms was dry and scaly. The tongue was bright red and glossy. There were no other significant observations.

Laboratory Data.—Frequent urinalyses showed a specific gravity of 1.004 to 1.014 and albuminuria, 2 to 4 plus. The urinary sediment contained occasional white blood cells and rare granular casts. The red blood cell count was 4,300,000 per cubic millimeter, and the hemoglobin content of the blood was 9 Gm. per hundred cubic centimeters. The sedimentation rate on two occasions was 14 and 45 mm. respectively per hour. The white blood cell count was 6,550 per cubic millimeter, with a normal differential count. Subsequent white cell counts varied between 4,500 and 9,000. The icterus index was 10. The plasma protein level was 7.3 Gm. per hundred cubic centimeters, later falling to 3.9 per hundred cubic centimeters. Examinations of stools gave positive results for blood for several days after her admission but then gave negative results. The nonprotein nitrogen on two occasions was 25 and 27 mg. per hundred cubic centimeters. A phenolsulfonphthalein test showed excretion of 67.5 per cent of the dye in two hours. A gastric analysis showed no free acid after the administration of histamine phosphate.

A series of gastrointestinal examinations showed a constant irregular narrowing of the pyloric antrum and a large duodenal cap measuring 7 by 7 cm. There was 50 per cent gastric retention after six hours. Roentgen examination after a barium sulfate enema showed no obstruction in the large intestine.

Course in the Hospital.—The patient was put on a Sippy regimen but continued to complain of epigastric and abdominal pain. After administration of barium by mouth marked intestinal hypotonia and fecal impaction developed, which were only partially relieved by vigorous measures. She persistently vomited everything taken by mouth.

The patient was transferred to the surgical service, where a laparotomy was performed. A bizarre, white, marble-like discoloration of the entire stomach and of the large and small intestines was found. It appeared to follow the longitudinal muscle fibers of the wall of the bowel and did not involve the mesentery. A mass was palpable in the greater curvature of the stomach, in the prepyloric region. Approximately three fourths of the stomach was removed by the Hofmeister technic.

Postoperatively the patient did poorly. She was unable to retain food. Fecal impaction again developed, and a cecostomy was performed nine days later. Despite all therapy her course continued down hill, and she died on her sixty-ninth day in the hospital.

From the Departments of Pathology of Grady Memorial Hospital and Emory University School of Medicine.

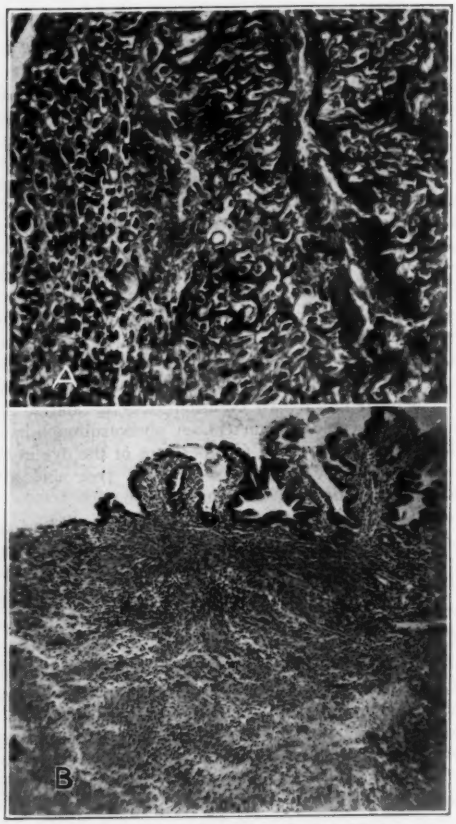
1. Koletsky, S., and Stecher, R. M.: Primary Systemic Amyloidosis, Arch. Path. **27**:267 (Feb.) 1939.

2. Pearson, B.; Rice, M. M., and Dickens, K. L.: Primary Systemic Amyloidosis, Arch. Path. **32**:1 (July) 1941.

An intravenous congo red test was performed three days before death. Sixty-five per cent of the dye was retained in the blood after one hour.

Morphologic Observations on Surgical Specimen.—Gross Observations.—On examination the serosa of the stomach was seen to consist of smooth, grayish white, glistening tissue, extending 2 to 3 mm. into the wall. When the stomach was opened, two superficial ulcerations of the mucosa, 1 and 1.5 cm. respectively in diameter, were found along the greater curvature, near the pylorus. The surrounding tissue was elevated but not indurated.

Histologic Observations.—Sections of the stomach were stained with phloxine–methylene blue, hematoxylin and eosin, congo red, crystal violet and iodine.



A, the muscular coat of the stomach. There is an increase of interstitial tissue caused by deposition of amyloid with resulting atrophy of muscle fibers. In this field the process varies from slight to fairly advanced in degree. Phloxine–methylene blue; × 400. *B*, gastric ulcer. There are marked fibrosis and inflammatory cell infiltration of the muscularis mucosae and the submucosa. The mucosa shows some repair. Hematoxylin-eosin; × 40.

Extensive and almost continuous amyloid deposits were found in the outer layers of the muscular coat and extending inward. They had caused atrophy and replacement of the greater portion of the musculature (fig. *A*). Less extensive patchy areas of amyloid deposits involved the distinctly hypertrophic muscularis mucosae. Other slight amyloid deposits were seen within the walls of the blood vessels, chiefly at the bases of the ulcerations. These ulcerations involved the muscularis mucosa but did not extend beyond it (fig. *B*). Their fundi and the adjacent tissue were heavily infiltrated by chronic inflammatory cells. Fibrosis of long standing was seen surrounding the ulcerations, and within this scar tissue a large number of partially or completely obliterated blood vessels were seen. The mucosa at the margin of the ulcers showed varying degrees of regeneration but no evidence of anaplasia. In the remaining portions of the stomach the mucosa showed considerable chronic inflammatory cell infiltration.

Diagnosis.—The diagnosis was amyloidosis of the stomach and two prepyloric ulcers.

Report of Autopsy.—Gross Observations: An autopsy was performed six hours after death. Permission was not granted for examination of the head. The body was fairly well developed but poorly nourished. There was pitting edema of the lower extremities. The operative incisions were in a poor state of healing.

When the peritoneal cavity was opened, the entire intestinal tract appeared bright red because of the extensive deposition of congo red dye. The remaining portion of the stomach, the duodenum and the terminal portion of the ileum showed extensive and diffuse involvement. The esophagus and the remaining portion of the intestinal tract, including the appendix, showed extensive but patchy deposits. The intestinal wall felt thickened and waxy. There were a few hemorrhages in the wall of the small intestine. Hemorrhages were more numerous in the wall of the descending colon. A sharp obstructing kink was found in the jejunum just distal to the gastrojejunal anastomosis, which was in good condition. The peritoneal cavity contained 1,000 cc. of clear yellow fluid. Localized peritonitis was present in the region of the abdominal incision. When the alimentary tract was opened, it was seen that the deposits of congo red were confined to the muscular coat and the muscularis mucosae. The mucosa throughout appeared normal, and no ulcerations were seen.

The heart weighed 290 Gm. Scattered throughout the endocardium, chiefly in the left auricle, were numerous small deposits of congo red, each 3 to 4 mm. across. Numerous small firm red nodules, 0.5 to 1 mm. in diameter, were present on the cusps and the annulus fibrosus of the mitral and tricuspid valves. A few small deposits were also seen in the proximal portion of the pulmonary artery. No other significant features were noted in the heart.

The spleen weighed 25 Gm. Its surface was firm and granular. The cut surfaces were deep purple, and the trabeculae were prominent.

No deposits of congo red were grossly visible in the liver, the spleen, the kidneys or the adrenal glands. A few deposits were noted in the splenic artery.

Other observations included pulmonary congestion, a moderately advanced degree of arteriosclerosis and chronic cholecystitis. No foci of tuberculosis or chronic suppuration were encountered.

Histologic Observations: Tissues were fixed in Zenker's fluid with 5 per cent acetic acid and in solution of formaldehyde (10 per cent concentration) U. S. P. The following stains were employed: phloxine–methylene blue and aniline blue routinely; congo red, Mayer's crystal violet—iodine reaction, Herxheimer's scarlet red and Turnbull's stain for iron on selected sections.

The heart showed numerous patchy areas of old scarring, with large deposits of amyloid. In these areas

there was atrophy of the myocardial muscular bundles without evidence of acute necrosis. These areas were most frequently encountered near the endocardial surface. In the auricles a large proportion of the musculature appeared to have been replaced by amyloid. A relationship between these lesions and extensive deposits of amyloid in the small arteries and arterioles was strongly suggested. Large deposits of amyloid were seen in the cusp and the annulus fibrosus of the mitral valve, which was otherwise normal.

The lungs showed early bronchopneumonia, edema and slight atelectasis and emphysema.

The spleen contained no amyloid. The red pulp was congested and showed some phagocytosis of the erythrocytes. An iron stain showed considerable accumulation of iron pigment within large mononuclear cells.

Extensive amyloid deposits were seen in the esophagus, the small and large intestines and the appendix. The process was almost entirely limited to the muscularis, with patchy involvement of the muscularis mucosae. The outer longitudinal musculature was constantly involved; the inner circular layer less frequently. In many areas the sequence of events could be traced in the patchy and later often confluent deposition of amyloid in the interstitial connective tissue, with subsequent atrophy of muscle fibers. There was no evidence of acute necrosis. Although many small arteries and arterioles contained medial deposits of amyloid, no definite relationship between these vessels and the diffuse interstitial deposits could be demonstrated.

In the pancreas some small amyloid deposits were seen in the walls of several small arteries and arterioles and in some of the small veins.

The liver showed marked congestion and fatty degeneration. Small deposits of amyloid were present in some of the branches of the hepatic artery, but no other amyloid was seen.

The kidneys showed peculiar tubular lesions, characterized by marked vacuolation of the epithelial cells of the distal convoluted tubules. These did not contain fat. There was moderate arteriosclerosis. No amyloid was present.

The adrenal glands were not remarkable except for some amyloid in several small arteries and in one large medullary vein.

The aorta displayed a moderate degree of arteriosclerosis. No amyloid was seen. The gallbladder showed some old scarring. No significant features were noted in the other organs, including the skeletal muscle, the bone marrow and the spinal cord.

The amyloid deposits described stained well with congo red, weakly with crystal and gentian violet and not at all with iodine.

Anatomic Diagnosis: The following diagnoses were made: primary amyloidosis of the esophagus, stomach, intestinal tract and heart and of the arteries of the pancreas, liver and adrenal glands; intestinal obstruction; ascites (1,000 cc.); recent subtotal gastrectomy; recent colostomy; localized peritonitis; early bronchopneumonia; pulmonary edema; congestion of the viscera; generalized arteriosclerosis; inactive chronic cholecystitis; emaciation.

COMMENT

Causation.—The causation of amyloid disease remains obscure. It appears to be a disease primarily of connective tissue. It can be reproduced in animals, principally the horse and the rabbit. In these animals the appearance of amyloid deposits is associated with a rise in the serum globulin.[3] Although usually the disease in human beings is not accompanied by demonstrable changes in the serum proteins, there is a more than coincidental association of amyloid disease with multiple myeloma, in which high globulin fractions are common. It has been suggested that deposition of amyloid substance results from a reaction of fixed tissue elements with a fraction of the serum globulin, perhaps on an allergic basis.[1]

This hypothesis receives support from the work of Hass and associates.[4] By fractionation of amyloid, a protein was found which was soluble between p_H 11 and p_H 12. The specific solubility appeared to be determined by a sulfate-bearing polysaccharide similar in properties to chondroitin-sulfuric acid. Different solubility properties were found in the amyloid of rabbits inoculated with tuberculin, horses receiving large doses of tetanus and human beings. Furthermore, differences were found in the amyloid in persons with tuberculosis and in persons with chronic osteomyelitis, as well as in animals under different causative circumstances. It was concluded that the properties of amyloid depend not only on the species but on the method or cause of production.

Types.—Human amyloid disease has been divided into four types: secondary amyloidosis, primary amyloidosis, amyloidosis associated with multiple myeloma and localized amyloid tumors.

Secondary amyloidosis occurs during the course of many chronic debilitating diseases, the most common being tuberculosis and chronic suppuration. The organs characteristically involved are the liver, the spleen, the kidneys and the adrenal glands, although small deposits may be found in any organ of the body. The amyloid deposits are usually clearly vascular and perivascular in distribution and generally stain well with congo red, crystal violet and iodine. In advanced stages the intravenous congo red test gives uniformly positive results.

Primary systemic amyloidosis occurs in the absence of predisposing diseases. The organs most frequently involved are the tongue, the

3. Reimann, H. A., and Eklund, C. M.: Long-Continued Vaccine Therapy as a Cause of Amyloidosis, Am. J. M. Sc. **190**:88 (July) 1935. Dick, G. F., and Leiter, L.: Experimental Amyloidosis and Hyperglobulinemia, Tr. A. Am. Physicians **52**:246, 1937. Reitstoetter, J.: Ueber die Goldzahl von normalem und pathologisch verändertem Blutserum, Ztschr. f. Immunitätsforsch. u. exper. Therap. **30**:468, 1920.

4. Hass, G. M.: Studies of Amyloid: II. The Isolation of a Polysaccharide from Amyloid-Bearing Tissues, Arch. Path. **34**:92 (July) 1942. Hass, G. M.; Huntington, R., and Krumdieck, N.: Amyloid: III. The Properties of Amyloid Deposits Occurring in Several Species Under Diverse Conditions, ibid. **35**:226 (Feb.) 1943.

heart, the stomach, the intestines, the skeletal muscles and the skin. Extensive deposits in the joints, tendons, bones, larynx, trachea, bladder and genitalia have also been reported. The liver, spleen, kidneys and adrenal glands usually contain little amyloid. The symptomatology depends on the organs involved. The average duration of the disease is two to three years, although in 1 case [1] it apparently persisted for fourteen years.

In most of the reported cases the amyloid deposits gave varying reactions with the usual specific staining technic, although positive reactions were obtained with at least one of the stains. Varying results were also obtained with the intravenous congo red test, many patients showing normal retention of the dye in the blood.

Amyloidosis associated with multiple myeloma is similar in distribution and staining characteristics to primary amyloidosis.

Localized amyloid tumors are occasionally seen in the larynx, tongue, eye, bladder and bones. They are usually solitary but may be multiple.

The case here reported seems to fill the necessary criteria for the diagnosis of primary systemic amyloidosis. The involvement was chiefly gastrointestinal, and there was moderate deposition in the myocardium and in the tricuspid and mitral valves. The parenchyma of the liver, spleen, kidneys and adrenal glands contained no amyloid. No foci of tuberculosis or chronic suppuration were encountered.

Points of Special Interest.—Several points are of special interest. Two ulcerations of the gastric mucosa were found in the operative specimen. These were obviously of long standing and may account for the patient's chief complaint. Gastric ulcers have been reported in but 1 other case of primary amyloidosis.[5] Here, too, hematemesis had occurred. The involvement of the heart valves seen in this case has been reported but twice before.[2] The intravenous congo red test, performed shortly before death, showed a normal retention of dye in the blood after one hour. This is in keeping with the observations of other authors.[1] The vital staining of all amyloid deposits in the body afforded by this intravenous test is perhaps unique in this case. The failure of the amyloid deposits to stain well with crystal violet and iodine is also in keeping with previous experience with this disease.

Of interest, also, is the long history of gastrointestinal complaints of this patient, dating back sixteen years before death. It seems reasonable to assume that the terminal intestinal hypotonia was due to massive replacement of the intestinal musculature by amyloid, but the relation of amyloid deposition to the patient's early symptoms cannot be determined.

SUMMARY

In a case of primary systemic amyloidosis with involvement chiefly of the alimentary tract the presenting clinical symptoms were those of gastric ulcer.

Intravital staining of the amyloid deposits following an intravenous congo red test, involvement of the heart valves and presence of gastric ulcerations are the unusual features of this case.

5. Lubarsch, O.: Zur Kenntnis ungewöhnlicher Amyloidablagerungen, Virchows Arch. f. path. Anat. **271**:867, 1929.

Progress in Internal Medicine

GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM JULY 1943 TO JUNE 1944

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CHICAGO

(Concluded from page 356)

COLON

Physiology.—Sheehan,[406] in discussing the effect of the autonomic nervous system on the physiologic functions of the gastrointestinal tract, considers the sympathetic and vagotonic manifestations as not distinctly separable but as called into play simultaneously in a selective manner. These manifestations may be either homeostatic or an expression of emotional behavior. When the autonomic response becomes excessive, symptoms result.

Krost[407] reports 2 fatal cases of generalized atony of the whole gastrointestinal tract in newborn infants; the condition was attributed to an unproved imbalance of the autonomic nervous system.

Mayoral[408] presents a case of tumor in the hypothalamic region in which "altered motility of the colon was observed fluoroscopically one month and eight days previous to death." The contractions were forceful and complete. The motor disturbance was attributed to the tumor.

Galambos,[409] in discussing the motility of the colon, presents a roentgenologic study of the large pendulum movement, with the conclusion that while it is not a regular physiologic process it is not necessarily abnormal. Redundancy and a long mesentery are necessary prerequisites. Hence volvulus and invagination may occur.

A comparative experimental and clinical study was made by Necheles and associates[410] of both the well known and the newer spasmolytic drugs: atropine sulfate, opium, belladona, papaverine hydrochloride, methylbiscyclohexylethylamine hydrochloride, tropic acid diethylaminoethyl-propionylbenzylalcohol hydrochloride, amyl nitrite, nitroglycerine, oil of peppermint, diphenylacetyldiethylaminoethanol and hexenyl-phenylacetyldiethylaminoethanol. Atropine and diphenylacetyldiethylaminoethanol were considered to be the most effective in the control of gastrointestinal symptoms. A similar study was made by Ingelfinger.[411]

In observing a series of 100 laparotomies, in which the patients were treated with neostigmine preoperatively and postoperatively, Koufman[412] found that those treated with neostigmine were more comfortable and had a greatly reduced incidence of intestinal distention.

Rats fed diets containing 10 and 20 per cent additions of lard, cottonseed oil, linseed oil, menhaden oil, Crisco, bayberry tallow, theobroma oil or tributyrin did not have diarrhea—not even when 2 cc. doses of castor oil were given by stomach tube.[413]

Wikoff, Gaul and Marks[414] in an excellent study of the effect of the glycerides of the saturated fatty acids on intestinal elimination in the dog, fed measured amounts of pure triglycerides mixed with a standard dog food. Constipation was produced by the feeding of diets containing 20 per cent additions of the triglycerides which

406. Sheehan, D.: Physiological Mechanisms Involved in Gastrointestinal Dysfunction, Psychosom. Med. **6**:56-57, 1944.

407. Krost, G. N.: Autonomic Nervous System Imbalance of the Whole Gastrointestinal Tract in the Newborn Infant, J. Pediat. **24**:635-640, 1944.

408. Mayoral, A.: Motor Changes Observed Fluoroscopically in the Colon of a Patient Afflicted with a Tumor in the Hypothalamic Region, Am. J. Digest. Dis. **10**:305-307, 1943.

409. Galambos, A.: Clinical and Radiological Observations Concerning the Large Pendulum Movement of the Colon, Am. J. Digest. Dis. **11**:151-158, 1944.

410. Necheles, H.; Olson, W.; Neuwelt, F., and Spier, E.: A Pharmacological and Clinical Study of Spasmolytic Drugs, Gastroenterology **2**:46-59, 1944.

411. Ingelfinger, F. J.: The Modification of Intestinal Motility by Drugs, New England J. Med. **229**: 114-122, 1943.

412. Koufman, W. B.: Control of Post-Operative Atonic Intestinal States with Prostigmin, Mil. Surgeon **93**:187-190, 1943.

413. Wikoff, H. L.; Koonce, S. D., and McGuire, H. J.: Some Effects of High Fat Diets on Intestinal Elimination, Am. J. Digest. Dis. **10**:266-270, 1943.

414. Wikoff, H. L.; Gaul, J. F., and Marks, B. H.: Some Effects of Diets Rich in the Glycerides of Saturated Fatty Acids on Intestinal Elimination, Am. J. Digest. Dis. **10**:395-399, 1943.

melted above 50 C. (tristearin and tripalmitin). The lipid content of the feces was greatly increased, the increase being much greater in neutral fat than in soap fat. The addition of 20 per cent trimyristin (melting point 48 to 50 C. uncorrected) did not affect the rate of elimination, although the neutral fat fraction was greatly elevated. The feeding of simple triglycerides of some of the saturated acids containing twelve or less carbons atoms (lauric, capric, caparyllic, caproic and butryic acids) produced laxative effects in all cases. The intensity of the action varied inversely with the number of carbon atoms and the melting point of the acid. As the cathartic action of the triglycerides increased, the percentage of added fat that the dogs would eat diminished. All the dogs ate the meals of standard dog food with the addition of 20 per cent trilaurin, but the concentration of added fat had to be reduced in the remainder of the cases. Tributyrin, having the most violent action of any of the fats fed, caused diarrhea in 1 dog when as little as 0.2 per cent was added to the standard food. Furthermore, this dog would not eat all the usual daily ration of a pound (0.5 Kg.) of the standard food after the addition of 0.2 per cent tributyrin.

Hurst [415] describes the normal defecation reflex as a mass movement of the feces from the colon into the rectum followed by expulsion due to voluntary contraction evoked by the sensation of a distended rectum. Rectal dyschezia is defined as a disturbance in the normal reflex with the collection of feces in the rectum. Megacolon is a dilatation of the rectum and pelvic colon with feces due to achalasia of the anal sphincter. Hurst advocates gradual rectal dilation as curative treatment. Delano,[416] on the other hand, takes the view that the term rectal dyschezia should be discarded because the rectal retention of feces occurs with and without organic disease and hence does not represent a clinical entity.

Gold and Zahm [417] describe a method for the comparison of laxative agents in constipated human subjects, show that the laxative efficacies of the fumarates of sodium, calcium and magnesium are the same and that these three substances also possess approximately the same laxative potency as sodium citrate and magnesium acid citrate gram for gram.

Hazelton and Talbert [418] state that the cathartic action of bile salts compound in mice is due to the content of cholic acid, agreeing with the clinical impression that other purified bile salts are not active as cathartics.

Tainter [419] reports that methyl cellulose is a synthetic material having physical and chemical properties suitable for use as a colloid laxative. In doses of 10 Gm. it approximately doubled the volume of the stools and increased their frequency. The toxicologic and clinical studies should be extended before its general therapeutic use is approved.

Spiesman [420] reviews the history of the rather unsuccessful attempts to change the intestinal flora by using Bacillus acidophilus, lactose and dextrin and discusses the use of colloidal kaolin and aluminum hydroxide gel in the treatment of colonic disorders.

Alvarez [421] analyzes the types of distress commonly due to constipation as well as those produced by strenuous purgation. Ingelfinger [422] and Palmer [423] each discuss the syndrome of the "irritable colon." Heilbrun [424] presents a case with extensive roentgenographic changes suggesting ileitis and colitis in which the only apparent ascribable cause was the daily use of cathartics for over twenty years.

Roentgenology.—Henderson,[425] in a well illustrated paper, discusses the technic of the roentgenologic examination of the colon and concludes that the "classic" barium sulfate enema is still the most generally useful method. The use of compression requires careful interpretation, for the observer may be easily misled. The

415. Hurst, A.: Dyschezia and Megacolon, Radiology **42**:128-135, 1944.

416. Delano, P. J., in discussion on Hurst,[415] pp. 190-191.

417. Gold, H., and Zahm, W.: A Method for the Evaluation of Laxative Agents in Constipated Human Subjects, with a Study of the Comparative Laxative Potency of Fumarates, Sodium Tartrate and Magnesium Acid Citrate, J. Am. Pharm. A. **32**:173-178, 1943.

418. Hazelton, L. W., and Talbert, K. D.: Further Studies on Cathartic Action in Mice: Senna, Aloe, Cascara, and Bile Salts, J. Am. Pharm. A. **33**:170-173, 1944.

419. Tainter, M. L.: Methyl Cellulose as a Colloid Laxative, Proc. Soc. Exper. Biol. & Med. **54**:77-79, 1943.

420. Spiesman, M. G.: Colloidal-Kaolin and Aluminum-Hydroxide Gel (Kalum*) in the Management of Lower-Bowel Conditions, Rev. Gastroenterol. **10**:191-200, 1943.

421. Alvarez, W. C.: Indigestion Due to Constipation, Gastroenterology **2**:427-431, 1944.

422. Ingelfinger, F. J.: Treatment of the "Irritable Stomach" and the "Irritable Colon," M. Clin. North America **27**:1385-1396, 1943.

423. Palmer, W. L.: Functional Disturbances of the Alimentary Tract, M. Clin. North America **28**:418-428, 1944.

424. Heilbrun, N.: Roentgen Evidence Suggesting Enterocolitis Associated with Prolonged Cathartic Abuse, Radiology **41**:486-491, 1943.

425. Henderson, N. P.: The Value of the Opaque Enema and Its Modifications, Brit. J. Radiol. **17**:140-149, 1944.

combined opaque enema and air inflation method is particularly helpful in diverticulosis; with other lesions this method may be misleading. Poppel and Bercow [426] describe a modified barium sulfate mixture, consisting of 75 Gm. of barium sulfate and 5 Gm. of acacia in 2 quarts (1.9 liter) of water, which permits the demonstration of not only the contour, as with the ordinary barium enema, but of the normally distended lumen and its contents. The method is considered of value particularly in the study of the region of the flexures and in cases in which there is considerable redundancy. Polyps and diverticula are more easily seen than with the ordinary barium sulfate enema. Wissing and Lowman [427] emphasize the importance of the lateral view, particularly in the sigmoid and lower descending colon.

Enteritis and Hepatitis.—Pollack and Gerber,[428] in a study of 88 cases of primary hepatic disease, found phlegmonous inflammation of the small or large intestine in 18. The lesion, apparently not previously described, has not been encountered by the authors in the past ten years except in association with primary disease of the liver, cirrhosis or toxic necrosis. The mechanism of production and the clinical significance are not yet clear. The intestine appears decidedly boggy. On microscopic examination there is "seen a diffuse phlegmonous inflammation of the intestinal wall characterized by an infiltration of all the layers of polymorphonuclear leukocytes." The lesions do not appear to bear a direct relation to the degree of hepatic inflammation.

Cecitis.—Spivack and Busch [429] report 2 cases of phlegmonous cecitis and collected 35 cases from the literature with a mortality of 8 per cent. Two types are described, circumscribed and diffuse. Phlegmonous cecitis is presented as a distinct disease entity attributed to enterogenous or hematogenous infection. The former is considered the more common and to result from mucosal abrasions from hard fecal masses, intestinal parasites or foreign bodies. Zieman [430] reports a case of foreign body, apparently a fish bone, perforating the cecum, with uneventful recovery following operation.

Rosser [431] reports 2 cases of simple ulcer of the cecum not associated with other recognized infections or tumefactions of the bowel. Less than 50 such cases have been described. The ulcer is usually found near the ileocecal valve on the mesial side of the cecum; it has a pronounced tendency to perforate and to cause extensive scarring and contraction. The symptoms are variable but usually suggest either appendicitis or cancer of the cecum and thus lead to surgical intervention. Frank and Doughty, in the discussion of this paper, each describe similar cases.

Nonspecific Ulcerative Colitis.—Alvarez and Bargen [432] emphasize the value of the sedimentation rate in the recognition of diarrhea due to organic disease. If the figure is low there is little chance that organic disease will be found, while if it is high, more than 40 or 50 mm. (Westergren method), there is almost certainly something seriously wrong with the bowel. They have also found the sedimentation rate helpful in estimating the extent or seriousness of colitis of the "thromboulcerative" variety. In patients in whom only the rectum and sigmoid segment are involved, the rate may be within normal limits.

An extract from the liver and lungs of patients with nonspecific ulcerative colitis contained a substance toxic and often lethal for mice.[433] Such a toxic factor was found in lesser amounts or in a milder form in an occasional control extract of stillborn infants but not in adult control lungs or infant livers.

An extensive study of patients with chronic ulcerative colitis disclosed that the majority had abnormal reactions to oral dextrose tolerance tests and that none of the reactions to intravenous dextrose tests were normal, although metabolism of dextrose as determined by basal metabolic rates and respiratory quotients was essentially normal.[434] A relatively small per cent of the patients had low fasting plasma vitamin A carotene and vitamin C levels. The prothrombin clotting time was prolonged in the majority of

426. Poppel, M. H., and Bercow, C.: The Use of a Modified Opaque Barium Sulfate Mixture in the Roentgenology of the Colon, Am. J. Roentgenol. **51**:727-729, 1944.

427. Wissing, E. G., and Lowman, R. M.: The Lateral View in the Roentgenologic Diagnosis of Lesions of the Colon, New England J. Med. **229**:207-210, 1943.

428. Pollack, A. D., and Gerber, I. E.: Abdominal Visceral Lesions Associated with Primary Disease of the Liver, Arch. Path. **36**:608-611 (Dec.) 1943.

429. Spivack, A. H., and Busch, I.: Phlegmonous Cecitis: Report of Two Cases and a Review of the Literature, Am. J. Surg. **61**:54-59, 1943.

430. Zieman, S. A.: Perforating Foreign Body of the Cecum, U. S. Nav. M. Bull. **41**:1103-1105, 1943.

431. Rosser, C.: Simple Penetrating Ulcer of the Cecum, Ann. Surg. **119**:377-383, 1944

432. Alvarez, W. C., and Bargen, J. A.: The Value of the Blood Sedimentation Rate in Recognizing Diarrheas Due to Organic Disease, Proc. Staff Meet., Mayo Clin. **19**:255, 1944.

433. Steiner, P. E.; Stanger, D. W., and Bolyard, M.: A Toxic Factor in the Tissues in a Case of Nonspecific Ulcerative Colitis, Proc. Soc. Exper. Biol. & Med. **55**: 8-10, 1944.

434. Bercovitz, Z., and Page, R. C.: Metabolic and Vitamin Studies in Chronic Ulcerative Colitis, Ann. Int. Med. **20**:239-254, 1944.

the patients. The results were all taken as evidence that the syndrome of chronic ulcerative colitis is not confined to an altered physiology of the colon but is also manifest by altered absorption and utilization, impairment of the insulin mechanism, generalized decreased capillary resistance and altered blood coagulation due to a decrease in prothrombin content.

Peters [435] reports chronic ulcerative colitis with complications including abdominal fistula, carcinoma of the cecum, renal insufficiency and pigmentation of the skin suggesting Addison's disease.

Sauer and Bargen [436] report 26 cases of ulcerative colitis complicated by carcinoma, thus bringing to 50 the number of such cases reported from the Mayo Clinic, an incidence of carcinoma of 2.5 per cent. In this group of 26, polyps were present in 15 (58 per cent). There were multiple carcinomas in 8, the greatest number in 1 person being eight primary carcinomatous lesions, all large enough to be diagnosed on roentgenologic examination.

Drueck,[437] on the basis of 3 cases of ulcerative colitis (1 of acute, 1 of chronic and 1 of recurrent colitis), advocates the use of iodoxyquinoline sulfonic acid in 2 per cent solution for colonic irrigation, and 4 to 8 grains (given by mouth) every six hours. Litvak and Levy [438] report a case of ulcerative colitis in a girl, aged 8½ years, in whom they thought quick improvement was brought about by the use of chiniofon. We recall, however, that over the past two decades chiniofon has been used extensively in treatment of this disease and abandoned.

Two fatalities in cases of chronic ulcerative colitis after an ileostomy are attributed to perforation of the ileum followed by peritonitis; hence it is suggested that ileostomy, if indicated, be performed at least 90 cm. above the ileocecal valve.[439] Peelen and Yonkman [440] describe severe diarrhea of the small intestine from an ileostomy. As therapy bismuth and opium were given orally without effect. A dramatic response apparently followed the administration of acetyl tannic acid and albumin tannate given in doses of 1 Gm. every four hours.

Miller [441] describes methemoglobinemia from bismuth subnitrate used in treatment of chronic ulcerative colitis. In forty-eight hours after use of the drug was stopped the level of methemoglobin in the blood decreased 80 per cent.

Amebiasis. — Diaz-Rivera and Rasberry [442] attribute the low reported incidence of amebiasis in Philadelphia to insufficient stool examinations and, until recently, lack of interest. Bews and Choquette [443] surveyed 500 unselected patients admitted to the Military Hospital at Ste. Anne de Bellevue, Quebec, and showed that 236 (47.2 per cent) of these had some form of protozoal cyst. Food handlers may be effective transmitters of the organism. Sawitz [444] recommends that before the diagnosis of amebiasis is excluded three stool specimens passed on alternate days should be examined followed by the examination of a stool after a saline cathartic and the examination of material obtained from the sigmoid on sigmoidoscopy. The unstained or hematoxylin-stained fecal film technics supplemented by the zinc sulfate centrifugal flotation method are recommended.

Continuous infection of children with amebiasis in a children's home suggested that the method of transmission of the infection was direct contact transfer aided by the general pollution of the environment.[445] Live steam sterilization of the environment combined with mass antiamebic chemotherapy constituted a simple and practical means of controlling the infection.

Jackman and Cooper [446] proctoscopically found ulceration of the amebic type in the lower part of the bowel in 20.8 per cent of 115 patients with amebiasis. Biopsy and scrapings from the ulcer at the time of proctoscopy afforded a positive diagnosis in 2 cases in which repeated examina-

435. Peters, G. A.: Chronic Ulcerative Colitis with Unusual Complications: Report of Case, Proc. Staff Meet., Mayo Clin. **19**:303-307. 1944.

436. Sauer, W. G., and Bargen, J. A.: Chronic Ulcerative Colitis Followed by Carcinoma: Report of Twenty-Six Cases, Proc. Staff Meet., Mayo Clin. **19**: 311-316, 1944.

437. Drueck, C. J.: Treatment of Chronic Ulcerative Colitis, Am. J. Digest. Dis. **11**:10-12, 1944.

438. Litvak, A. M., and Levy, H.: Non-Specific Ulcerative Colitis—Case Report and Review of the Literature, Arch. Pediat. **61**:293-299, 1944.

439. Crandon, J. H.; Kinney, T. D., and Walker, I. J.: Perforation of the Ileum Following Late Ileostomy for Ulcerative Colitis, New England J. Med. **230**:419-421, 1944.

440. Peelen, M., and Yonkman, F. F.: Tannin Control of Ileostomy, Am. J. Digest. Dis. **10**:277-278, 1943.

441. Miller, R. C.: Methemoglobinemia Occurring in a Case of Chronic Ulcerative Colitis, Proc. Staff Meet., Mayo Clin. **19**:308-311, 1944.

442. Diaz-Rivera, R. S., and Rasberry, E. A.: Amebiasis: Analytical Study of Cases Admitted to a Philadelphia Hospital During the Last Five Decades, Am. J. M. Sc. **207**:754-755, 1944.

443. Bews, D. C., and Choquette, L. P. E.: A Preliminary Study of the Incidence of the Intestinal Protozoa in the Canadian Armed Forces, Canad. M. A. J. **49**:501-503, 1943.

444. Sawitz, W. G.: The Diagnosis of Amebiasis, Clinics **2**:828-841, 1943.

445. Ivanhoe, G. L.: Studies on the Transmission of Amebiasis in a Children's Home in New Orleans, Am. J. Trop. Med. **23**:401-419, 1943.

446. Jackman, R. J., and Cooper, W. L.: Value of Proctoscopy in the Diagnosis of Amebiasis, Am. J. Digest. Dis. **10**:365-366, 1943.

tions of the stools had given negative results. Anal inflammatory lesions, such as abscess and fistula, occurred in only 1.7 per cent of the cases, in striking contrast with the high percentage of such lesions observed in cases of chronic ulcerative colitis and regional ileitis. The importance of a proctoscopic examination to rule out other disease, such as neoplasm, occurring independent of the amebiasis is indicated by the finding in 1 case of a carcinoma in the lower sigmoid in a patient who had not improved clinically after amebicidal therapy.

Jorge [447] and his collaborators report acute amebic abscess of the liver and acute peritonitis due to intestinal perforation. Dysentery had been present three years before the onset of the acute illness. Results of examinations of stools were negative for organisms but amebas were found in the wall of the abscess. In spite of intensive treatment with emetine hydrochloride and sulfapyridine, vioform and arsenicals, as well as surgical drainage of the abscess, perforation of the colon occurred, leading to death from acute peritonitis. Numerous ulcerations were found in the colon. Trophozoites were present in the walls of the intestinal ulcerations.

The successful local treatment with penicillin of an amebic abscess of the liver secondarily infected with beta hemolytic streptococci of Lancefield group G is described.[448]

Other Parasites.—Raifman [449] reports another case of infection with Isospora bigemina, also described by Bustos. The patient was treated, with good results; but we must point out that such infections are known to be self limited.

Lowe,[450] in reporting 16 cases of human infection with Strongyloides stercoralis, found that gentian violet medicinal gave symptomatic relief, but neither it nor the other drugs tried, emetine hydrochloride, fuadin (stibophen) and antimony and potassium tartrate, could be considered satisfactory agents for eradicating the infection.

Wallace and Chamberlin [451] report that in the treatment of hookworm infection tetrachloroethylene administered orally is satisfactory in the majority of cases. Intraduodenal administration gives better results but should be reserved for refractory cases, because the oral method is usually satisfactory and the intraduodenal method is time consuming. Lowe [452] studied 363 cases of mild hookworm infection in patients with malaria. When the eosinophil count was greater than 1,350 cells per cubic millimeter helminth infection was almost certainly present. Cutaneous lesions, dyspepsia and pronounced eosinophilia without anemia were produced by the hookworm infection, in contrast with the manifestations of malaria.

Hsu [453] examined stool specimens from 720 persons in northwest China. The lowest incidence of infection with helminths was 40.21 per cent and the highest 70.42 per cent; the majority of the parasites were Ascaris lumbricoides. The highest incidence of Endamoeba histolytica infection was 2.43 per cent.

Fernando and Balasingham [454] review 162 cases of acute ascariasis. The mortality was 27 per cent in patients with ascariasis alone and 50 per cent in patients in whom ascariasis was complicated by other diseases. Acute symptoms followed anthelmintic therapy in 18 per cent of cases. Symptoms of acute gastroenteritis were the presenting feature in 53 per cent and those of an "acute abdomen," chiefly partial intestinal obstruction, in 20.9 per cent. The acute gastroenteritis or partial obstruction should be treated before anthelmintic therapy is given.

Most [455] found phenothiazine in doses of 30 mg. per kilogram of body weight given for three days an effective drug in the treatment of human Enterobius vermicularis infection but ineffective against infections with Ascaris lumbricoides, Necator americanus, Strongyloides stercoralis and Trichocephalus. The drug was safe in therapeutic dosage, but toxic doses resulted in hemolytic anemia and hepatitis.

Elliott [456] also recommends phenothiazine.

Sisk [457] emphasizes that when one member of a household is infected with pinworms all other

447. Jorge, J. M.; Goñi Moreno, I., and Peralta, A. R.: Consideraciones sobre un caso de amebiasis grave, Rev. Asoc. méd. argent. **57**:707-709, 1943.

448. Noth, P. H., and Hirshfeld, J. W.: Amebic Abscess of the Liver with Secondary Infection: Local Treatment with Penicillin, J. A. M. A. **124**:643-646 (March 4) 1944.

449. Raifman, J.: A Case of Human Parasitosis Caused by the Isospora Bigemina, Rev. Gastroenterol. **10**:279-282, 1943.

450. Lowe, T. E.: Strongyloidiasis in Man: Infestation with Strongyloides Stercoralis (Bavay, 1876), M. J. Australia **1**:429-435, 1944.

451. Wallace, W. C., and Chamberlin, D. T.: Hookworm Infestation: Comparative Methods of Treatment, Mil. Surgeon **93**:427-432, 1943.

452. Lowe, T. E.: Hookworm Infestation, M. J. Australia **1**:289-292, 1944.

453. Hsu, K. C.: Human Intestinal Parasites in Northwest China: A Brief Survey, Chinese M. J. **61**: 292-295, 1943.

454. Fernando, P. B., and Balasingham, S.: Acute Ascariasis in Children, Indian J. Pediat. **10**:149-173, 1943.

455. Most, H.: Studies on the Effectiveness of Phenothiazine in Human Nematode Infections, Am. J. Trop. Med. **23**:459-464, 1943.

456. Elliott, M.: Phenothiazine in the Treatment of Human Intestinal Helminthic Infestations, Tr. Roy. Soc. Trop. Med. & Hyg. **37**:163-164, 1944.

457. Sisk, W. N.: The Modern Treatment of Pinworm Infections, North Carolina M. J. **5**:52-55, 1944.

members can usually be shown to be infected if one uses the cellophane swab technic. A minimum of seven swabs should be examined before one can be reasonably sure that the patient is not infected. Sisk has never succeeded in ridding a household of pinworms when one or more members refused to take the treatment. Treatment with gentian violet medicinal is reasonably satisfactory provided it does not cause too much nausea. Phenothiazine gives results equal, if not superior, to those obtained with gentian violet, although it also is somewhat toxic and must be used with care. Whichever treatment is used, the only way to be certain of cure is to take at least seven swabs from each member of the family, three about one week after treatment and four more two weeks later. About 60 per cent of the families will be cured on the first treatment, about half of the remaining 40 per cent on the second treatment and the remaining 20 per cent on the third treatment if it is taken.

Megacolon.—McKell [458] reports 2 cases of so-called anal achalasia with megacolon in which symptomatic relief was obtained with neostigmine and ergotamine tartrate administered orally. Hawksley [459] reports 12 cases of Hirschsprung's disease in children from 2 to 11 years of age treated with spinal (nupercaine) anesthesia repeated two or three times. Six patients were cured, 5 improved and in 1 no modification was observed.

In a careful analysis of congenital megacolon, the cases of 29 patients on whom subtotal colectomy was performed are reported; of these, 24 were males.[460] Seven of the 29 (24.1 per cent) died as a result of the operation. Follow-up studies were made on 16, the results being considered excellent in 13 and good in 3. Subtotal colectomy is considered the treatment of choice in cases of segmental congenital idiopathic megacolon due to chronic mechanical obstruction. It is also indicated for persons with severe megacolon, for persons not responding to spinal anesthesia, and for male patients. Except in emergencies it is contraindicated for infants. Johnson and Benson [461] report megacolon in a boy aged 2 years, observed proctoscopically to have a stricture of unknown origin 10 cm. above the anus, narrowing the lumen to 3 mm. The megacolon disappeared after removal of the stricture. Martin and Ward [462] report a case of megacolon in which volvulus necessitated resection of the transverse colon followed by resection of the remainder of the colon for an associated inflammatory stricture of the sigmoid and anastomosis of the terminal portion of the colon.

Obstruction.—Zaslow [463] reports obstruction of the large bowel in 2 newborn infants due to congenital bands extending from the under surface of the liver to the hepatic flexure of the colon and calls attention to the similarity of the symptoms to those of obstruction of the large bowel in adults, namely, abdominal distention out of proportion to the amount of vomiting. Bueermann [464] and Dennis [465] give brief discussions of the diagnosis and surgical management of obstructive lesions of the colon.

Traumatic Rupture.—Cameron [466] and associates made an interesting and well illustrated study of the abdominal injuries due to underwater explosion. Twenty patients were submitted to operation, with a mortality of 50 per cent. Retroperitoneal and subserous hemorrhages occurred in all patients. Perforation of the cecum was present in 9 and of the ileum in 7, and multiple perforations were present in 4. Late perforations occurred in 2, a result probably of hemorrhage initiated by the primary injury. A late survey of 80 who recovered without operation showed that the commonest symptom was abdominal pain persisting from three days to three months. Melena was present in 82 per cent of these patients and in some persisted for four months. In 20 per cent a history of hemoptysis was reported, and in 14 per cent, hematemesis. An experimental investigation with 16 goats was made. Eight of them had their chest and abdomen immersed and 8 had only the abdomen immersed. Intestinal lesions were common in both types. Bleeding by

458. McKell, J.: Anal Achalasia with Megacolon in Children Treated Successfully with "Prostigmin" and Ergotamine Tartrate, M. J. Australia **1**:465-466, 1944.

459. Hawksley, M.: Spinal Anaesthesia in the Treatment of Hirschsprung's Disease with Reports of Twelve Cases, Brit. J. Surg. **31**:245-252, 1944.

460. Whitehouse, F.; Bargen, A. J., and Dixon, G. F.: Congenital Megacolon: Favorable End Results of Treatment by Resection, Gastroenterology **1**:922-937, 1943.

461. Johnson, J. R., and Benson, R. E.: The Surgical Treatment of Megacolon with Report of a Case of Acquired Megacolon, Proc. Staff Meet., Mayo Clin. **19**: 324-328, 1944.

462. Martin, J. D., Jr., and Ward, C. S.: Megacolon Associated with Volvulus of the Transverse Colon, Am. J. Surg. **64**:412-416, 1944.

463. Zaslow, J.: Obstruction of the Large Bowel in Newborn Infants Due to Congenital Bands, J. Pediat. **23**:337-339, 1943.

464. Bueermann, W. H.: Obstructive Lesions of the Colon: Diagnosis and Surgical Management, Northwest Med. **42**:311-315, 1944.

465. Dennis, C.: Treatment of Large Bowel Obstruction: Transverse Colostomy Incidence of Incompetency of Ileocecal Valve; Experience at the University of Minnesota Hospitals, Surgery **15**:713-734, 1944.

466. Cameron, G. R.; Short, R. H. D., and Wakeley, Cecil P. G.: Abdominal Injuries Due to Under-Water Explosion, Brit. J. Surg. **31**:51-66, 1943.

rectum and mesenteric hemorrhages were more severe when the abdomen alone was immersed. Gill and Hay,[467] in a series of 16 such cases, operated on 6 patients, 4 of them dying. Two of the remaining patients died without operation. Martin [468] reports the bizarre case of a 28 year old seaman thrown into the water after a cruiser was torpedoed. A depth charge exploded near him. Perforation of the rectum occurred as a primary event in a single organ, with no evidence of other abdominal injury. Death from peritonitis ensued.

Hicken and Carlquist [469] discuss rupture of the gastrointestinal tract due to nonpenetrating injuries, report 6 cases and emphasize the frequency with which this condition occurs. Delayed perforation occurred in 60 per cent of the cases and was not recognized until peritonitis occurred. Collins [470] reports 3 more cases, further illustrating the necessity of careful observation and early exploration. Brown [471] reports a spontaneous perforation of the pelvic colon, and Swenson and Harkins [472] describe traumatic rupture of the rectum caused by compressed air.

Seybold, Black and Jackman,[473] in discussing injuries to the rectum by impalement, describe the case of a 3 year old boy who had sat down forcibly on the shank of a bicycle seat. Proctoscopic examination disclosed a hole in the anterior wall of the rectum in the region of the rectovesical space. This was repaired through an abdominal incision. Five grams of sulfathiazole crystals were placed in the pelvis. Combined gas gangrene and tetanus antitoxin was given intramuscularly. The child made an uneventful recovery. Of 7 such patients treated in the presulfonamide era, 2 died and 5 recovered.

Diverticulitis.—Young and Young [474] review the literature and analyze 84 cases of diverticulitis. Casper,[475] in 489 studies with barium sulfate enema observed 5 cases of localized irritability and spasticity of the proximal portion of the sigmoid, interpreted as a localized inflammation and thought to represent a clinical entity. In the single fatal case, death resulted from peritonitis. Autopsy showed the walls of the rectum, sigmoid and distal descending colon noticeably thickened, edematous, grayish red and friable. No definite ulcerations were seen. The roentgenograms in the 5 cases are all suggestive of either diverticulitis without demonstrable diverticula or so-called nonspecific ulcerative colitis, leading Casper to question the existence of sigmoiditis as an entity. Thunig [476] reports diverticulitis of the sigmoid complicated by perforation mistaken for carcinoma and successfully resected, with subsequent reestablishment of the continuity of the colon.

Lymphogranuloma Venereum.—Seidenstein [477] concludes that anorectal manifestations of lymphogranuloma seem to be best treated by prolonged systemic and local therapy with sulfonamide drugs combined with at least one course of Frei antigen intravenously. Napp [478] presents an interesting study of the disease. Bodkin [479] attributes the difficulty in the passage of stools to the prolapse of the rectal wall into the stricture on straining and describes a surgical procedure for its correction.

Polyposis.—McLaughlin [480] reviews diffuse polyposis and collected 30 cases in the literature between 1937 and 1942, bringing the total number of such cases to 331. David,[481] in emphasizing the importance of destroying or removing polyps, states that many can be handled by fulguration or local removal but more radical surgical measures may be indicated. Keller [482] describes an instance in which local excision of a degenerated polyp on the posterior wall of the lower part of the rectum effected an apparent cure.

467. Gill, W. G., and Hay, C. P.: A Clinical Study of Injuries of the Abdomen Due to Under-Water Explosion, Brit. J. Surg. **31**:67-73, 1943.

468. Martin, P. G. C.: Perforation of Rectum from Immersion Blast, Lancet **2**:605-606, 1943.

469. Hicken, N. F., and Carlquist, J. H.: Traumatic Rupture of the Gastro-Intestinal Tract by Non-Penetrating Forces, Am. J. Surg. **64**:209-216, 1944.

470. Collins, A. N.: Traumatic Rupture of the Intestine, Minnesota Med. **27**:276-278, 1944.

471. Brown, J.: Spontaneous Perforation of the Pelvic Colon, Brit. J. Surg. **31**:307-308, 1944.

472. Swenson, S. A., Jr., and Harkins, H.: Rupture of the Rectosigmoid by Compressed Air: Case Report, Am. J. Surg. **63**:141-143, 1944.

473. Seybold, W. D.; Black, B. M., and Jackman, R. J.: Impalement of the Rectum, Proc. Staff Meet., Mayo Clin. **19**:224-227, 1944.

474. Young, E. L., and Young, E. L., III: Diverticulitis of the Colon: A Review of the Literature and an Analysis of Ninety-One Cases, New England J. Med. **230**:33-38, 1944.

475. Casper, S. L.: Sigmoiditis, Am. J. Roentgenol. **50**:24-32, 1944.

476. Thunig, L. A.: Complicated Diverticulitis of the Sigmoid: Case Report, Am. J. Surg. **64**:386-399, 1944.

477. Seidenstein, H. R.: Rectal Stricture Due to Lymphogranuloma Venereum, Surgery **14**:73-82, 1943.

478. Napp, O. E.: Estrechez linfogranulomatosa rectosigmoidea, Prensa méd. argent. **30**:2224-2234, 1943.

479. Bodkin, L. G.: Stricture of the Rectum, Am. J. Surg. **61**:277-279, 1944.

480. McLaughlin, C. W., Jr.: Diffuse Polyposis of the Large Intestine, Am. J. Surg. **62**:258-266, 1943.

481. David, V. C.: The Management of Polyps Occurring in the Rectum and Colon, Surgery **14**:387-394, 1943.

482. Keller, D. R.: Carcinoma of the Rectum, Am. J. Surg. **64**:346-351, 1944.

Endometriosis. — Ben-Asher [483] reviews the literature of endometriosis of the rectosigmoid, discusses the pathology, diagnosis, roentgenologic manifestations and treatment and reports the case of a 37 year old woman who gave a history of periodic pains in the lower part of the abdomen associated with diarrhea, aggravated during the menstrual period, followed by obstipation with ribbon-like stools. Sterility and menstrual disorders were present. On sigmoidoscopic examination an obstruction was found at about 6 inches (15 cm.) but without a lesion of the mucosa. The barium sulfate enema showed a constant filling defect in the region of the sigmoid, with regular borders and an intact but puckered mucosa. At the operation a mass was found involving the entire circumference of the bowel for 1½ inches (3.8 cm.), an endometrial cyst of the ovary and endometriosis of the mesovarium. The uterus, both ovaries and both tubes were removed; nothing was done with the tumor of the sigmoid. Three years later the patient was reported as having gained 24 pounds (10.9 Kg.) in weight, and a barium enema disclosed no evidence of a filling defect of the sigmoid. Smith,[484] on the other hand, reports a patient treated by resection of the involved colon followed by castrating doses of high voltage roentgen therapy.

Carcinoma.—Cave [485] notes that the Bureau of Vital Records and Statistics of the city of New York, with a population of 7,300,000 in the year 1942, showed that 1,962 persons died from cancer of the stomach, 1,616 died of cancer of the colon and 911 of cancer of the rectum. The value of the more frequent use of the sigmoidoscope and the x-ray for patients with the slightest suspicion of a disturbed gastrointestinal tract is emphasized.

Seefeld and Bargen [486] studied with extreme care the lymphatic, perineural and venous spread of 100 specimens of rectal carcinoma resected at Mayo Clinic during the years 1935 and 1936, finding lymphatic invasion in 47 per cent of the cases, perineural invasion in 30 per cent, and venous invasion in 20 per cent. The incidence of invasion increased with the degree of malignancy. Metastasis to lymph nodes was observed in 67 per cent of the cases with perineural involvement and in 85 per cent of those with venous involvement. Pain was a prominent symptom in 89 per cent of the cases with perineural invasion. Local recurrence was found in 27, with neural involvement in 22.7 per cent, venous involvement in 11.1 per cent, involvement of both sorts in 25.9 per cent and of neither sort in 40.7 per cent. In 4 cases of local recurrence, metastasis to lymph nodes occurred without invasion of nerves or veins and in 7 cases without histologic evidence of spread by any of the three routes. Visceral metastatic lesions were present at operation or developed later in 94 per cent of the cases with venous involvement, whereas they were found in only one fifth of this frequency in cases without venous invasion. Singleton [487] gives a good description of the blood supply, and Whipple [488] outlines the surgical treatment of the terminal ileum, cecum and right colon.

Connor and Harvey,[489] in analyzing the important symptoms and signs in 50 cases of carcinoma of the right side of the colon, found abdominal pain and weakness common symptoms. Occult blood was seen in the stools in 75 per cent of the cases, and a palpable tumor was noted in 82 per cent. In 8 cases the diagnosis was not made preoperatively.

Bertin [490] concludes that metastasis from cancer of the digestive tract to bone is more common than is generally realized, the bones of the trunk being the most frequent sites. The lesions are usually osteolytic and may obtain considerable size before producing symptoms. Roentgen therapy had no effect in the 3 cases described. Beilin [491] reviews the features of 117 cases of cancer of the rectum. Guzman [492] reports that lymphogranuloma was associated with cancer of the rectum and genitals in 8 of 12,546 cancerous patients observed during a ten year period. One case is described in which the rectum and vulva were involved by both diseases.

The incidence of multiple malignant lesions has been reported to be between 3 and 5 per cent.

483. Ben-Asher, S.: Endometriosis of the Rectosigmoid: Report of a Case with a Review of the Literature, Am. J. Digest. Dis. **11**:141-144, 1944.

484. Smith, R. S.: Endometrioma of the Sigmoid, Northwest Med. **42**:192-195, 1943.

485. Cave, H.: Cancer of the Colon, Bull. New York Acad. Med. **20**:255-263, 1944.

486. Seefeld, P. H., and Bargen, J. A.: The Spread of Carcinoma of the Rectum: Invasion of the Lymphatics, Veins, and Nerves, Ann. Surg. **118**:76-90, 1943.

487. Singleton, A. O.: The Blood Supply of the Large Bowel with Special Reference to Resection, Surgery **14**:328-341, 1943.

488. Whipple, A. O.: Surgery of the Terminal Ileum, Cecum and Right Colon, Surgery **14**:321-327, 1943.

489. Connor, G. J., and Harvey, S. C.: The Diagnosis of Carcinoma of the Right Colon, Yale J. Biol. & Med. **16**:289-300, 1944.

490. Bertin, E. J.: Metastasis to Bone as the First Symptom of Cancer of the Gastro-Intestinal Tract: Report of Three Cases, Am. J. Roentgenol. **51**:614-622, 1944.

491. Beilin, D. S.: Clinical Features, Diagnosis and Treatment of Carcinoma of the Colon and Rectum, Radiology **42**:539-544, 1944.

492. Guzman, L.: Co-Existence of Chronic Lymphogranuloma and Cancer, Radiology **41**:151-156, 1943.

McCormick [503] finds that during a three year Many of these are synchronous or multicentric malignant lesions. Multiple asynchronous primary malignant lesions are less frequent. Lichtman [493] reports 1 case in which three primary malignant lesions developed in the colon in the course of seventeen years and a second which involved the removal of coincident primary carcinomas of the rectum and lung. Sheinfeld and Rudolph [494] found 2 cases of multiple primary malignant tumors involving the gastrointestinal tract and 1 involving the breast and gallbladder in 128 cases of malignant disease. In 110 surgical specimens of malignant disease of the gastrointestinal tract there were 2 synchronous malignant growths. The 3 cases reported include 1 in which there were two apparently independent carcinomas involving the cecum and the transverse colon. The other 2 cases consist of 1 of squamous cell carcinoma of the esophagus and an adenocarcinoma of the stomach and another of adenocarcinoma of the esophagus and adenocarcinoma of the stomach.

McGauley [495] discusses the advantage of a high operation rate over the maintenance of a low postoperative mortality rate and shows that from the standpoint of the number of patients alive one year after operation the former is preferable. Allen [496] thinks that the term "resectability" should be substituted for "operability." In his own series 91 per cent of the lesions were resectable. The mortality and morbidity were directly related to resectability. Of the first 50 patients reported on by Murdock [497] for whom radical resection of the left side of the colon and the rectum was done only 1 was over 70 years of age and the mortality was 4 per cent. The subsequent acceptance of more patients of advanced age increased the mortality to 9.3 per cent, from which Murdock concludes that a considerable increase in mortality must be expected in the case of patients over 70. Cattell [498] reports that 81.4 per cent of 172 patients were submitted to resection for carcinoma of the colon and rectum during 1941, with a mortality of 5 per cent. A one stage abdominoperineal resection was done in 76.7 per cent of the cases of rectal carcinoma, with a mortality of 3.8 per cent. The modified Mickulicz resection was performed for carcinoma of the colon, with a mortality of 2.7 per cent.

Coller and Ransom,[499] in comparing the results of operation in cases of carcinoma of the rectum observed during the last six years with those observed during the preceding six years, found that operability increased owing to earlier diagnosis, extension of the limits of operability, standardization of the operative technic and improvement in the preoperative and postoperative management. Mayo and Twyman [500] reported a follow-up study made in 90 cases of carcinoma of the rectum in which the patients survived a one stage combined abdominoperineal resection. At the end of three years 61 of the patients were alive and 29 dead. Eleven operations were considered palliative. Even though obvious metastasis to the liver or deep aortic nodes existed at the time of the operation, 45 per cent of the patients survived three years or more. Dixon [501] describes the technic used in 206 cases of carcinoma low in the sigmoid and the rectosigmoid, 181 of which were performed with a view of cure and 25 as a palliative procedure. The operative mortality rate was reduced from 19.4 to 2.4 per cent. This result was attributed to the careful preoperative treatment. In the operative procedure the superior hemorrhoidal vessels were sacrificed without apparent impairment of the circulation of the rectosigmoid or rectum.

Allen [502] reports 7 cases of peritonitis secondary to perforation of carcinoma of the colon. Perforations are most likely to occur in the fungating type of adenocarcinoma either at the site of the tumor or in the loop of bowel just proximal. The diagnosis should be suspected for any patient of cancer age who shows evidence of peritoneal inflammation. The treatment is drainage first and resection later, but the prognosis is poor.

493. Lichtman, A. L.: Multiple Primary Malignant Lesions, Proc. Staff Meet., Mayo Clin. **19**:317-323, 1944.

494. Sheinfeld, W. I., and Rudolph, I.: Multiple Primary Carcinomas of the Gastrointestinal Tract, Surgery **15**:579-589, 1944.

495. McGauley, F. F.: Carcinoma of the Large Bowel, New York State J. Med. **43**:1727-1731, 1943.

496. Allen, A. W.: Carcinoma of Colon, Surgery **14**:350-365, 1943.

497. Murdock, R. L.: Cancer of the Left Colon and Rectum, South. M. J. **36**:685-691, 1943.

498. Cattell, R. B.: Carcinoma of the Colon and Rectum: A Report of 503 Patients Treated at the Lahey Clinic 1938-1941, Inclusive, Surgery **14**:378-386, 1943.

499. Coller, F. A., and Ransom, H. K.: Carcinoma of the Rectum: Conclusions Based on Twelve Years' Experience with Combined Abdominoperineal Resection, Surg., Gynec. & Obst. **78**:304-315, 1944.

500. Mayo, C. W., and Twyman, R. A.: One Stage Combined Abdominoperineal Resection for Carcinoma of the Rectum: Results of Three Year Follow-Up Survey in Ninety Cases, Proc. Staff Meet., Mayo Clin. **18**:438-443, 1943.

501. Dixon, C. F.: Anterior Resection for Carcinoma Low in the Sigmoid and the Rectosigmoid, Surgery **15**: 367-377, 1944.

502. Allen, P. D.: Peritonitis Secondary to Perforation in Carcinoma of the Colon, New York State J. Med. **43**:1732-1735, 1943.

503. McCormick, N. A.: Cancer of the Rectum, Radiology **42**:531-538, 1944.

period 74 per cent of the patients with rectal cancer were advised to have an abdominoperineal resection; 6 per cent refused. In 80 per cent of those operated on resection was done; in 16 per cent the lesion was too far advanced and in 4 per cent death followed cecostomy for intestinal obstruction. Preoperative roentgen irradiation was usually given. For the patients with inoperable cancer irradiation was used routinely; colostomy was necessary for only 42 per cent of these.

Stenstrom and Malbin [504] report on 173 patients with cancer of the rectum treated by radiation therapy; 92 of these were inoperable; 12 refused operation; 69 underwent resection but were treated with radiation also because of the likelihood of incomplete removal. Five of the last group were first thought inoperable. Of the patients treated by resection followed by irradiation 34 per cent survived five years or more. Of 104 treated by radiation alone or with colostomy 5 survived five years; the average length of life was twenty-one months.

In dogs 900 r may lead to ulceration and perforation of the rectum.[505] In a review of 195 cases of cancer of the rectum and sigmoid treated by radiation the conclusion is reached that roentgen ray therapy is of value in freeing a fixed cancer preoperatively and as a palliative measure for patients with inoperable cancer.

Carroll [506] describes a deodorant containing charcoal and phenylsalicylate for use with colostomies.

Lymphosarcoma.—Harper, Waugh and Dockerty,[507] in reporting on lymphosarcoma of the cecum, emphasize that apparently inoperable lesions may be lymphosarcomatous and hence can be treated by resection and irradiation. Winkelstein and Levy [508] report 15 cases of lymphosarcoma of the intestine, describe the proctoscopic picture and consider the differentiation between small round cell and reticulum cell tumors to be unimportant clinically. Even with surgical removal plus radiotherapy the disease is invariably fatal, the duration of life being usually less than one year, although 1 of their patients lived six years.

Miscellaneous.—The literature of fecal fistula is reviewed, with a discussion of its classification, incidence and cause and a report on 590 patients observed at the Mayo Clinic in a twelve year period.[509]

Ducassi and Bargen [510] report the unusual case of a 28 year old woman who gave the history of bleeding from the vagina on one day followed by hemoptysis continuing for one or two days and followed by rectal bleeding, the amount of blood passed by rectum varying from a teaspoonful to a pint (500 cc.) at a time. Aside from hemorrhoids no rectal lesion was found.

Pemberton and Brindley [511] report on a stenosing superficially ulcerated lesion of the rectum which when resected and examined histologically was found to be inflammatory, with typical noncaseating tubercles. Culture and smears prepared with carbolfuchsin did not demonstrate the presence of tubercle bacilli, but nevertheless the presumptive diagnosis seemed to be primary tuberculosis of the rectum.

Shucksmith [512] discusses the treatment of anorectal conditions in the Army and recommends the use of caudal anesthesia in operative measures for fissure, hemorrhoids, anorectal abscess and fistula. Cantor [513] on the basis of 32 cases recommends tattoo-neurotomy as the procedure of choice for so-called cryptogenic pernicious pruritus ani.

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